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

The mechanism or mechanisms driving atopic asthma initiation: The infant respiratory microbiome moves to center stage

Patrick G. Holt, DSc, FRCPath, FRCPI, FAA *Perth and Brisbane, Australia*

Developments over the last 5 to 10 years, principally from studies on comprehensively phenotyped prospective birth cohorts, have highlighted the important role of viral respiratory tract infections during infancy and early childhood, particularly those occurring against a background of pre-existing sensitization to perennial aeroallergens, in driving the development of early-onset atopic asthma. Although debate surrounding the mechanism or mechanisms governing this causal pathway remains intense, demonstration of the capacity of pretreatment with anti-IgE antibody to blunt seasonal virus-associated asthma exacerbations in children provides strong support for the underlying concept. However, emerging data appear set to further complicate this picture. Notably, a combination of culture-based studies and complementary population-wide bacterial metagenomic data suggests that parallel host-bacteria interactions during infancy might play an additional role in modulating this causal pathway, as well as contributing independently to pathogenesis. These and related issues surrounding development of immune competence during the crucial early postnatal period, when these pathways are maximally active, are discussed below. (J Allergy Clin Immunol 2015;136:15-22.)

Key words: *Asthma, atopy, infancy, viral infections, nasopharyngeal microbiome*

Discuss this article on the JACI Journal Club blog: www.jaci-online.blogspot.com.

It is increasingly recognized that the cause and pathogenesis of allergic disease involve multiple factors beyond the classical IgE-associated inflammatory mechanisms traditionally thought of as its defining hallmarks. Moreover, it is also now acknowledged that key events that determine risk for development of chronic allergic disease frequently occur many years in advance of manifestation of persistent symptoms. Recognition of these facts represents an important watershed in the continuing saga of allergy drug development because they markedly alter perceptions of the range of potential therapeutic targets and the available relevant treatment (particularly preventive treatment) windows. This review focuses on atopic asthma as an archetypal example of allergic disease and examines in particular the role of early childhood factors in the underlying pathogenic process.

Abbreviations used

AMDC:	Airway mucosal dendritic cell
ARI:	Acute respiratory illness
CAS:	Childhood Asthma Study
DC:	Dendritic cell
fLRI:	Febrile lower respiratory tract illness
HrV:	Human rhinovirus
LRI:	Lower respiratory tract illness
mDC:	Myeloid dendritic cell
MPG:	Microbial profile group
pDC:	Plasmacytoid dendritic cell
PNA:	Postnasal aspirate
RSV:	Respiratory syncytial virus
Treg:	Regulatory T

ALLERGIC SENSITIZATION TO AEROALLERGENS: WHEN, WHERE, AND HOW?

The initial priming of T_H2 memory that underlies expression of allergic symptoms resulting from ongoing exposure to aeroallergens in adults can be tracked back to early childhood in most cases. Cross-sectional studies in the 1990s first demonstrated age-dependent increases in serum titers of aeroallergen-specific IgE in children, which in many cases appeared to begin increasing during the first few years of life.[1,2] A variety of evidence (reviewed by Holt[3]), particularly demonstration of the presence of apparently aeroallergen-specific T_H2 cells in cord blood,[4-6] suggested that initial priming of relevant T_H2 memory can in many cases occur *in utero*. However, follow-up studies on the responding T cells identified them as immunologically naive ***recent thymic emigrants*** with functionally immature antigen receptors that enabled them to bind (and as a consequence become transiently activated by) specific aeroallergens.[7] The majority of responsive recent thymic emigrant cells undergo rapid apoptosis after activation and do not apparently give rise to long-lived memory cells, although a small subset can be

From the Telethon Kids Institute, University of Western Australia, Perth, and Queensland Children's Medical Research Institute, University of Queensland, Brisbane.

The author is funded by the National Health and Medical Research Council of Australia.
Disclosure of potential conflict of interest: P. G. Holt declares that he has no relevant conflicts of interest.
Received for publication March 13, 2015; revised April 30, 2015; accepted for publication May 7, 2015.

Corresponding author: Patrick G. Holt, DSc, FRCPath, FRCPI, FAA, Division of Cell Biology, Telethon Kids Institute, PO Box 855, West Perth 6872, Western Australia. E-mail: Patrick.Holt@telethonkids.org.au.

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2015.05.011

Terms in boldface and italics are defined in the glossary on page 16.

"rescued" by ***common γ-chain*** cytokines if present at sufficiently high levels within the local microenvironment.[7] Further studies suggested that stable T_H2 memory generation does not usually commence until around the second half of postnatal year 1.[8]

More recent studies on serum IgE antibodies in infants and young children have reignited debate on this question based on claims that aeroallergen-specific IgE of fetal as opposed to maternal origin can be detected at low levels in cord blood by using highly sensitive assay methodology.[9] However, the evidence supporting the fetal origin of this antibody is indirect, and its validity has been challenged by other evidence.[10] Moreover, prospective tracking of postnatal IgE titers in serum of individual members of a large birth cohort using samples collected repeatedly over the first 5 years of life strongly suggests that IgE antibody production against aeroallergens rarely begins before age 6 months.[8,11] Additionally, these studies demonstrate that a prominent feature of these early IgE responses is that they occur, at least initially, in almost all subjects, including those who remain nonatopic throughout subsequent childhood.[11] In these latter subjects IgE titers typically wax and wane cyclically within the concentration range of 0.01 to 0.35 kU/L (ie, less than the accepted sensitization threshold). Based on evidence from the experimental literature,[12,13] this cycling process reflects underlying competition between allergen-specific T_H2 and regulatory T (Treg) cell populations within individual aeroallergen-specific memory responses. In nonatopic subjects this cross-regulatory process is eventually dominated by Treg cells, and as a result, T_H2 cell proliferation is terminated and aeroallergen-specific "tolerance" is established, accompanied by waning of downstream specific IgE production, which in many cases is permanent.

The cellular mechanism or mechanisms that govern this competition for tolerance/sensitization to aeroallergens has been partially elucidated. The key cell population in this context is the network of airway mucosal dendritic cells (AMDCs) responsible for local immune surveillance, which were first described in the Holt laboratory[14,15] and subsequently further characterized by many other groups (reviewed by Holt et al[16] and Lambrecht and Hammad[17]). These cells are responsible for transmission of

GLOSSARY

CCR2: A gene that encodes 2 isoforms of a receptor for monocyte chemoattractant protein 1 (CCL2), a chemokine that specifically mediates monocyte chemotaxis. Monocyte chemoattractant protein 1 is involved in monocyte infiltration in patients with inflammatory diseases, such as rheumatoid arthritis, as well as in the inflammatory response against tumors and inflammatory responses in the lung.

COMMON γ-CHAIN (γ_c OR CD132): Also known as IL-2 receptor subunit γ (IL-2RG), the common γ-chain is a cytokine receptor subunit common to the receptor complexes for the following interleukin receptors: IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 receptors. The γc glycoprotein is a member of the type I cytokine receptor family expressed on most lymphocyte populations, and its gene is found on the X-chromosome of mammals.

FCR: A protein found on the surfaces of certain cells, including B lymphocytes, follicular dendritic cells, natural killer cells, macrophages, neutrophils, eosinophils, basophils, and mast cells, that contributes to the protective functions of the immune system. Fc receptors bind to antibodies that are attached to infected cells or invading pathogens. Their activity stimulates phagocytic or cytotoxic cells to destroy microbes or infected cells.

FCεRI: The high-affinity receptor for the Fc region of IgE, an antibody isotype involved in allergy disorders and parasitic immunity. FcεRI is a tetrameric receptor complex consisting of 1 α (FcεRIα, antibody-binding site), 1 β (FcεRIβ, which amplifies the downstream signal), and 2 disulfide bridge–connected γ chains (FcεRIγ, the site where the downstream signal initiates). It is constitutively expressed on mast cells and basophils and is inducible in eosinophils. A different form is expressed on myeloid cells, comprising 1 α and 2 γ chains.

HUMAN TYPE I INTERFERONS: A large subgroup of interferon proteins that help regulate the activity of the immune system. The mammalian types are IFN-α, IFN-β, IFN-κ, IFN-δ, IFN-ε, IFN-τ, IFN-ω, and IFN-ζ. IFN-α and IFN-β are secreted by many cell types, including lymphocytes (natural killer [NK] cells, B cells, and T cells), macrophages, fibroblasts, endothelial cells, osteoblasts, dendritic cells, and others. They stimulate both macrophages and NK cells to elicit an antiviral response and are also active against tumors.

IFN-γ: Also known as type II interferon, IFN-γ is a cytokine that is critical for innate and adaptive immunity against viral, some bacterial, and protozoal infections. It is an important activator of macrophages and inducer of MHC class II molecule expression. IFN-γ is produced predominantly by natural killer and natural killer T cells as part of the innate immune response and by CD4 T_H1 and CD8 cytotoxic T lymphocyte effector T cells once antigen-specific immunity develops. The importance of IFN-γ in the immune system stems in part from its ability to inhibit viral replication directly and most importantly from its immunostimulatory and immunomodulatory effects.

IL-12: A cytokine produced by dendritic cells and macrophages in response to Toll-like receptor stimulation. IL-12 is involved in the differentiation of naive T cells into T_H1 cells. It is known as a T cell–stimulating factor, which can stimulate the growth and function of T cells. It stimulates the production of IFN-γ and TNF-α from T cells and natural killer cells, and reduces IL-4–mediated suppression of IFN-γ.

MHC CLASS II MOLECULES: A family of molecules found mainly on antigen-presenting cells, such as dendritic cells, mononuclear phagocytes, some endothelial cells, thymic epithelial cells, and B cells. Antigens presented by class II peptides are derived from extracellular proteins, which are acquired by means of endocytosis or phagocytosis, and loading of fragments of processed protein antigens onto MHC class II molecules occurs intracellularly after biochemical processing of the antigens.

MYELOID DENDRITIC CELL (MDC): An antigen-presenting cell most similar to monocytes, which act as messengers between the innate and adaptive immune systems by processing antigen and presenting it on the cell surface to the T cells of the immune system. mDCs are major stimulators of T cells and secrete IL-12.

PBMC: Any blood cell having a round nucleus (as opposed to a lobed nucleus). Comprised of lymphocytes, monocytes, macrophages, and dendritic cells, these blood cells are a critical component in the immune system to fight infection.

PLASMACYTOID DENDRITIC CELL (PDC): Cells with certain characteristics similar to mDCs but that look like plasma cells. pDCs produce high amounts of IFN-α and play a key role in defense against microbial infections.

RECENT THYMIC EMIGRANTS: T cells that first exit the thymus in a phenotypically and functionally immature state. In particular, they express antigen receptors that lack the fine specificity of those on mature T cells, and as a result, they bind a much broader range of peptides.

16S RNA GENE DEEP SEQUENCING: A common sequencing method used to identify and compare bacteria present within a given sample that has become a well-established method for studying phylogeny and taxonomy of samples from complex microbiomes or environments that are difficult or impossible to study.

The Editors wish to acknowledge Kristina Bielewicz for preparing this glossary.