Clinical reviews in allergy and immunology

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B-lymphocyte lineage cells and the respiratory system

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List of Design Committee Members: Atsushi Kato, PhD, Kathryn E. Hulse, PhD, Bruce K. Tan, MD, and Robert P. Schleimer, PhD

Activity Objectives

1. To understand the development and differentiation of B lymphocytes.
2. To understand the transcription factors, mediators, and signaling pathways involved in B-lymphocyte maturation.
3. To describe the role of B lymphocytes and immunoglobulins in diseases of the respiratory tract.

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Adaptive humoral immune responses in the airways are mediated by B cells and plasma cells that express highly evolved and specific receptors and produce immunoglobulins of most isotypes. In some cases, such as autoimmune diseases or inflammatory diseases caused by excessive exposure to foreign antigens, these same immune cells can cause disease by virtue of overly vigorous responses. This review discusses the generation, differentiation, signaling, activation, and recruitment pathways of B cells and plasma cells, with special emphasis on unique characteristics of subsets of these cells functioning within the respiratory system. The primary sensitization events that generate B cells responsible for effector responses throughout the airways usually occur in the upper airways, tonsils, and adenoid structures that make up the Waldeyer ring. On secondary exposure to antigen in the airways, antigen-processing dendritic cells migrate into secondary lymphoid organs, such as lymph nodes, that drain the upper and lower airways, and further B-cell expansion takes place at those sites. Antigen exposure in the upper or lower airways can also drive expansion of B-lineage cells in the airway mucosal tissue and lead to the formation of inducible lymphoid follicles or aggregates that can mediate local immunity or disease. (J Allergy Clin Immunol 2013;131:933-57.)

Key words: *B cells, plasma cells, plasmablasts, respiratory diseases*

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Along with the skin and gastrointestinal tract, the respiratory tract is a large surface that interacts extensively with the environment outside the body. The exposed area of the respiratory tract is huge; in human subjects it has a surface area of 500 m^2, which is roughly the size of a tennis court.[1] Because large volumes of air are moved through the respiratory system rapidly and constantly, there is considerable exposure to airborne organisms that might cause pathology. The nose performs a filtering role, and many bacteria, viruses, and fungi are deposited there. Innate immune responses include passive mechanisms, such as formation of a mucus blanket, mucociliary removal, and swallowing of particles and constitutive expression of host defense molecules by airway epithelium and submucosal glands. Also at play are active innate responses, such as receptor-mediated activation of

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Abbreviations used

AID: Activation-induced cytidine deaminase
APRIL: A proliferation-inducing ligand
BAFF: B cell–activating factor of the TNF family
BAL: Bronchoalveolar lavage
BCMA: B-cell maturation antigen
BCR: B-cell receptor
BLNK: B-cell linker protein
BTK: Bruton tyrosine kinase
CD40L: CD40 ligand
COPD: Chronic obstructive pulmonary disease
CRS: Chronic rhinosinusitis
CRSwNP: Chronic rhinosinusitis with nasal polyps
CSR: Class-switch recombination
CTD: Autoimmune connective tissue diseases
CVID: Common variable immune deficiency
DC: Dendritic cell
EBI2: EBV-induced molecule 2
ERK: Extracellular signal-regulated kinase
GC: Germinal center
GOLD: Global Initiative for Chronic Obstructive Lung Disease
HEV: High endothelial venule
HP: Hypersensitivity pneumonitis
iBALT: Inducible bronchus-associated lymphoid tissue
IC: Immune complex
ILF: Isolated lymphoid follicle
iNOS: Inducible nitric oxide synthase
IPF: Idiopathic pulmonary fibrosis
IRF: Interferon regulatory factor
LN: Lymph node
MAPK: Mitogen-activated protein kinase
MyD88: Myeloid differentiation primary response gene–88
MZ: Marginal zone
NALT: Nasopharynx-associated lymphoid tissue
NF-κB: Nuclear factor κB
NIK: Nuclear factor κB–induced kinase
OB: Obliterative bronchiolitis
OVA: Ovalbumin
PI3K: Phosphoinositide 3-kinase
pIgR: Polymeric immunoglobulin receptor
PIP_3: Phosphatidylinositol-3,4,5-triphosphate
PKC: Protein kinase C
PLCγ2: Phospholipase Cγ2
PP: Peyer patch
RA: Rheumatoid arthritis
SHM: Somatic hypermutation
sIgA: Secretory IgA
SLE: Systemic lupus erythematosus
SLO: Secondary lymphoid organ
STAT: Signal transducer and activator of transcription
SYK: Spleen tyrosine kinase
TACI: Transmembrane activator and CAML interactor
T_{FH}: Follicular helper cells
TLR: Toll-like receptor

release of host defense molecules by epithelial cells, alveolar macrophages, and other cells; activation of glandular secretion; recruitment of phagocytic cells to the airways; and exudation of vascular fluids. These responses provide a robust defense against all but the most aggressive of potential pathogens. Frequently, innate immune responses do not deter microorganisms, and adaptive immune responses must be marshaled to maintain the integrity of airway function and survival of the host. Adaptive immune responses in the airways are mediated by B and T cells that express highly evolved and specific receptors. In some cases, such as autoimmune diseases or inflammatory diseases caused by excessive exposure to self-antigens or foreign antigens, these same immune cells can cause disease by virtue of overly vigorous responses.

The purpose of this review is to discuss the cells of the B-cell lineage and their role in disease and immunity in the respiratory system. We discuss the generation, differentiation, signaling, activation, and recruitment pathways of B cells and plasma cells, with special emphasis on unique characteristics of subsets of these cells functioning within the respiratory system. There are some important differences between human subjects and mice, the most studied species, with respect to the organization of B cell–containing tissues and responses (Table I). Nonetheless, much of the best information on the molecular and cellular pathways used by B cells has been derived in the mouse. Likewise, there is considerable information on the natural history of B-lineage cells in the gastrointestinal tract, probably because the vast majority of total bodily antibody production occurs in the gut. Although our greatest interest is in the role of B cells and plasma cells in human airways disease, we have frequently incorporated findings and interpretations that arise from study of the mouse, the gastrointestinal tract, or both, although we have tried not to burden the review by qualifying all such references.

Another important point to make is that B cells have been associated with immunoglobulin responses since their discovery and distinction from T cells in the middle of the 20th century. Although immunoglobulin production remains the most recognized, most studied, and probably most important function of B cells, we would be remiss if we did not point out that impressive recent studies have demonstrated many important roles of B cells that are independent of immunoglobulin production, such as roles in antigen presentation and as regulatory cells akin to regulatory T cells. Very little is known about either of these functions in the respiratory system. We have mentioned these activities where information is available but have focused primarily on immunoglobulin responses. Finally, although there have been a few very valuable reviews of B cells and the respiratory system published, it has become abundantly clear that the study of B-cell biology in the respiratory system, especially in human subjects, is an exceedingly important subject that yearns for significantly more investigation.[2-4]

OVERVIEW OF THE ADAPTIVE IMMUNE RESPONSE AND IMMUNOGLOBULIN PRODUCTION

B-cell lineages

The majority of B cells develop from lymphoid progenitor cells in the specialized microenvironment of the bone marrow. Early stages of this process are dependent on contact between the developing B-cell precursors and bone marrow stromal cells but do not require antigen. These developmental steps revolve around functional rearrangement of the B-cell receptor (BCR), are tightly regulated by positive and negative selection steps, and result in the formation of immature B cells that are licensed to traffic to peripheral lymphoid tissues. A detailed discussion of this process is beyond the scope of this review but has recently been elegantly presented elsewhere.[5] An overview of the important structural organization of immune tissues and events that occur in the selection and expansion of B-lineage cells in the airways is provided