Immunology

Elina Toskala, MD, PhD

Background: **Knowledge of our immune system functions is critical for understanding allergic airway disease development as well as for selection of appropriate diagnostic and therapeutic options for patients with respiratory allergies.**

Methods: **This review explains the current understanding of the basic immunology of the upper airways and the pathophysiology of allergic responses, including the mechanisms behind allergic rhinitis.**

Results: **The immune system can be divided to 2 main defense systems that function differently—innate immunity and adaptive immunity. Innate immunity includes several defensive mechanisms such as anatomic or physical barriers, physiological barriers, phagocytosis, and inflammation. The adaptive immune response is activated in an antigen-specific way to provide for the elimination of antigen and induce lasting protection. Hypersensitivity reactions occur when an exaggerated adaptive immune response is activated. Allergic rhinitis is an example of a type I, immunoglobulin E, mediated hypersensitivity reaction.**

Conclusion: **Today we have several immunomodulatory treatment options for patients with allergic airway diseases, such as subcutaneous and sublingual immunotherapy. An understanding of the basics of our immune system and its method of functions is key for using these therapies appropriately.** © 2014 ARS-AAOA, LLC.

Key Words:
immunology; allergy; upper airways; allergic rhinitis; airway allergy

***How to Cite this Article*:**
Toskala E. AAOA allergy primer: immunology. *Int Forum Allergy Rhinol.* 2014;4:S21–S27.

Immune system

The immune system is the body's protection system from infectious agents and other harmful substances. It is constantly adjusting and developing to our environment. This system includes many different effector cells and molecules that have a specific role in the system. The main 4 tasks of our immune system are as follows: (1) immunological recognition; (2) immune effector function; (3) immune regulation; and (4) immunological memory.[1]

The immune system can be divided to 2 main defense systems that function differently—innate (native or natural) immunity and adaptive (acquired or specific) immunity. Innate immunity is of ancient origin and responds rapidly on exposure to infectious organisms, whereas the adaptive immune system takes days to develop but is often more effective. Both response mechanisms depend on activation of leucocytes originating from the bone marrow.[1,2]

Innate immunity protects us in various ways. It uses several different types of defensive barriers: anatomic or physical barriers; physiological barriers; phagocytic barriers; and inflammatory barriers. All these defenses are present with or without stimulation, they have limited specificity, they are not enhanced by repeated exposure. and they have limited diversity of expression.[1]

Recent studies have shown that innate immunity directs the adaptive immune system by providing early signaling with cytokines, thus allowing lymphocytes to develop and mount pathogen-specific or inflammatory immune responses.[3] The initial adaptive immune response is activated when the barriers of the innate immune response have been breached. This activation happens in an antigen-specific way to provide for the elimination of a specific antigen and induce lasting protection. Lymphocytes (T cells and B cells) and antigen-presenting cells (APCs) (macrophages, B cells, and dendritic cells) form the basis of adaptive immunity. This system is specific for particular antigens; it

Department of Otolaryngology–Head and Neck Surgery, School of Medicine, Temple University, Philadelphia, PA

Correspondence to: Elina Toskala, MD, PhD, Dept. of Otolaryngology–Head and Neck Surgery, Temple University, School of Medicine, 3440 North Broad Street, Philadelphia, PA 19140; e-mail: elina.toskala@temple.edu

Potential conflict of interest: None provided.
Knowledge of our immune system functions is critical for understanding allergic airway disease development as well as for selection of appropriate diagnostic and therapeutic options for patients with respiratory allergies. This review explains the current understanding of the basic immunology of the upper airways and the pathophysiology of allergic responses, including the mechanisms behind allergic rhinitis (AR).

Received: 28 June 2014; Revised: 30 June 2014; Accepted: 1 July 2014
DOI: 10.1002/alr.21380
View this article online at wileyonlinelibrary.com.

expresses immunological memory, has diversity in specificity, and is capable of self/non-self recognition. Additionally, it has a self-limiting capacity to decrease an immune response.

Both the innate and the adaptive immunologic systems operate together and interact. They augment each other through antibodies, complement, and cytokines. Antibodies and complement enhance phagocytosis, antibodies activate complement, and cytokines stimulate adaptive and innate responses.

Cell types and their roles in immunity

Myeloid lineage

Cells from the myeloid lineage contribute to the innate immunity system. Macrophages, which reside in most tissues in the body, are mature forms of the monocytes that circulate in blood and subsequently migrate to tissues and differentiate. Macrophages and monocytes both are phagocytes, which are capable of ingesting foreign particles. Other myeloid cells include granulocytes (neutrophils, eosinophils, and basophils) and dendritic cells. Macrophages are relatively long-lived cells and play several roles in both innate and adaptive immunity. They engulf and kill invading microorganisms and subsequently transfer the pathogens and infected cells to the adaptive immune response. They also help to induce inflammation and secrete signaling proteins to activate and recruit other cells to the inflammation site.[1]

There are 3 different types of granulocytes: eosinophils, basophils, and neutrophils. They have densely staining granules in their cytoplasm, and are also called polymorphonuclear leucocytes. They have a short survival time of only a few days. Neutrophils are the most numerous and most important granulocytes that are phagocytic and activate bactericidal mechanisms. Eosinophils and basophils are important in the defense against parasites that are too large to be ingested by macrophages as well as in the allergic inflammatory reactions. Mast cells differentiate in the tissues and are best known for their role in mediating allergic reactions. Dendritic cells are phagocytic cells with finger-like processes that have their main role in antigen uptake and presenting antigens to T lymphocytes.[1]

Lymphoid lineage

Lymphoid progenitor cells differentiate into natural killer (NK) cells, B lymphocytes, T lymphocytes, and plasma cells. Each of these cell types is important in adaptive immunity. Lymphocytes are derived from stem cells residing in the bone marrow. Bone marrow and the thymus gland are the primary lymphoid organs of the immune system. After differentiation into a lymphoid lineage, they become functional by passage through either the thymus (T cells) or the bone marrow (B cells). Both have surface member–receptors designed to bind specific antigens. Naive B cells are coated with immunoglobulin M (IgM) and IgD, which are both membrane-bound immunoglobulins that have 2 heavy and 2 light chains in their structure. The variation in these chain structures enables the production of different antigen-specific immunoglobulins that are capable of binding unprocessed antigens.[1]

All lymphocytes express clusters of differentiation, although they differ according to the specific type of lymphocyte lineage. Surface receptors are pertinent to the function and uniqueness of lymphocytes. These structures allow for recognition of self from non-self, identification of unique antigenic determinants, and identification of populations of cells. T lymphocytes uniquely express T-cell antigen receptors (TCRs) on their surface. TCRs are composed of α-chains and β-chains and bind to peptides presented by APCs. B lymphocytes bind antibodies to their cell surface via F_c receptors, which stand ready to stimulate the cell to proliferate and differentiate into plasma cells, thus producing large amounts of immunoglobulins. The third type of lymphocyte, NK cells, are large granular cells that recognize certain tumors and virus-infected cells.

The role of the thymus gland is to mature primitive T cells into cells that can distinguish self from non-self. Primitive lymphoid T cells enter the thymus devoid of any cell-surface antigen receptors (TCRs) or cellular markers (CD4, CD8). These cells are induced to express common cell markers (CD1, CD2, CD5, CD6, CD7, and CD25), which are necessary during early ontogeny. Within the cortex of the thymus, these progenitor T cells undergo rearrangement of genes (a, b, g, or d) within the TCR; different arrangement of the TCR genes constitute the CD configuration). Cell-surface expression of the TCR is dependent upon formation of a complex with CD3. As the T cells further develop within the thymus, positive and negative selection occurs, resulting in mature T lymphocytes that can distinguish self from non-self in the context of major histocompatibility complex (MHC) molecules. This maturation process occurs either by cytokine expression or cell-to-cell contact and is directed by cortical cells of the thymus. Two major groups of T cells emerge: CD4 T helper cells or CD8 T cytotoxic cells.

Activation and isotype switching are the processes by which B cells produce antigen-specific antibodies, which is a multistep process under the control of T helper type 2 (Th2) CD4 cells through both cell-to-cell antigen presentation and expression of interleukins. Switch regions within the heavy chain DNA gene sequences are modified in order to specify IgG, IgE, or IgA subtypes. Antigen-specific B cells then differentiate into either plasma cells that can produce antibodies or memory cells that remain in the body for surveillance of the antigens, in order to more quickly stimulate the production of specific immunoglobulins.

Antigen responses

Antigens are foreign bodies that can be soluble or particulate and are capable of eliciting an immune response. They react with lymphocytes to induce the formation of

antibodies or sensitized cells. Lymphocytes are the only immune cells that are capable of recognizing specific antigenic determinants, or epitopes, and thus are responsible for the adaptive immunologic responses of memory and specificity. Each lymphocyte is able to identify only 1 epitope. Each cell during development encodes its receptors by rearranging DNA to fabricate a unique antigen receptor. That cell and all of its clones therefore express receptors that are specific to that antigen. An antibody can have a direct effect in neutralizing an antigen, but in other cases antibody binding to antigen stimulates the complement cascade to eradicate the antigen or activate other inflammatory cells to respond.

Complement is an essential component of the immune system. It has a role in both specific and nonspecific immune responses to infection. Complement is a series of proteins that act in a cascading fashion, each step acting as a catalyst for the next. The end result is lysis of the target cell. There are 2 main pathways for activation of complement. The classic pathway (adaptive) is activated by formation of antigen-antibody complexes. The alternate pathway (innate) is activated by interaction with microbial surfaces. The complement system mechanisms of action include opsonization and phagocytosis, direct lysis of microorganisms, and chemoattraction of inflammatory cells.

Antibodies

Humoral immunity is mediated by antibodies synthesized by B lymphocytes and secreted by their fully differentiated end cells, the plasma cells. This arm of immunity is a defense mechanism against extracellular agents. It consists of T cell–dependent and T cell–independent responses. Follicular B cells present MHC-restricted protein antigens and receive T cell help that promotes immunoglobulin class switching, affinity maturation, and memory differentiation. These antigen responses are referred to as T cell–dependent. Large antigens that have repeating antigenic determinants, such as carbohydrates in cell wall and capsules of bacteria cannot be presented in MCH class II molecules and therefore induce T cell–independent response.

The antibodies (immunoglobulins) are glycoproteins composed of polypeptides (82–96%) and carbohydrates (4–18%) and are secreted by activated B cells. All immunoglobulin molecules consist of 2 identical 50-kDa heavy chains and 25-kDa kappa or lambda light chains that vary in amino acid sequence from one antibody to another; these chains are named V_H, V_κ, and V_λ. The juxtaposition of 1 V_H segment and 1 V_κ or V_λ segment creates the antigen-binding portion of the immunoglobulin molecule and each immunoglobulin molecule has 2 identical antigen-binding sites. The carboxyl terminal portions of the heavy and light chains are constant in each subclass of antibody. The heavy chain constant regions pair to form the Fc domain of the molecule, which is responsible for the most of the effector functions of the immunoglobulin molecule, including binding Fc receptors and activating complement.[2]

Although all antibody molecules that are secreted by a single clone of B lymphocytes will have identical isotypes, the B cell is induced to make new classes, or isotypes, of immunoglobulin in response to cytokine-directed instructions from the TH2 cell. The progression of new antibody isotypes produced by B cells is defined by the sequence of constant domain coding in the B lymphocyte DNA, designed with a different effector function in mind. Just as the 3-dimensional structure of the idiotype defines antigen specificity, the sequence of amino acids in the constant domains of the immunoglobulin molecule (isotype) dictates the effector functions that will be expressed.

The TH2 activation of B lymphocytes causes intense proliferation in the germinal centers, and somatic hypermutation may cause slight variation in the shape of the idiotype. Clonal selection of the idiotype with highest affinity for antigen results in affinity maturation.

IgM

IgM is the first isotype of antibody that can be produced by the body. It exists in serum as a pentamer held together by a joining (J) chain. It constitutes approximately 10% of serum immunoglobulins. The functions of IgM are (as a monomer) receptor on B cells, antigen capture in the secondary lymphoid organs, and (as a pentamer) in plasma, activation of complement.

IgG

IgG is the major isotype produced after IgM. It constitutes approximately 75% of serum immunoglobulins and exists in four subisotypes (IgG1, IgG2, IgG3, and IgG4). It activates complement, opsonizes, mediates antibody-dependent cell-mediated cytotoxicity (ADCC), and is actively transported across the placenta.

IgA

IgA constitutes approximately 15% of serum immunoglobulins. It is the major isotype produced in the submucosa, colostrum, and the breast milk. It is a dimer with a J chain holding it together and it functions in inhibiting the binding of substances to cells or mucosal surfaces. It does not activate complement or mediate opsonization. Secretory IgA is transported into the lumen of the gastrointestinal, respiratory, or genitourinary tracts by binding to the poly-immunoglobulin receptor. This receptor is retained as protection from proteolytic cleavage of IgA. IgA provides the primary defense mechanism against local mucosal infections.

IgE

IgE is the antibody that binds to mast cells, is responsible for antihelminthic and allergic responses and can mediate antibody-mediated cellular cytotoxicity. It accounts for only 0.004% of the total serum immunoglobulins and normally exists as a monomer. Cross-bridging of IgE molecules on the surface of mast cells and basophils by antigen

triggers release of mediators from these cells and lead to an allergic reaction.

IgD

IgD constitutes 0.2% of the total serum immunoglobulins and exists as a monomer. It functions as a membrane-bound antigen receptor on the B cell surface.

Hypersensitivity reactions

Hypersensitivity reactions occur when an exaggerated adaptive immune response is activated. These reactions are the result of normally beneficial immune responses that act inappropriately and cause inflammatory reactions and subsequent tissue damage. Hypersensitivity reactions do not occur on first contact with an antigen, but usually appear on subsequent exposure. These reactions are classified as type I to type IV hypersensitivity reactions. They all have different types of hypersensitivity reactions and the cellular and humoral components that they involve differ.

Type I (Immediate) hypersensitivity reaction

Type I (Immediate) hypersensitivity reaction is mainly mediated by IgE-antibodies and mast cells. It is manifested within minutes of re-exposure to an antigen. An antigen crosslinks 2 IgE-antibodies on a mast cell, leading to its degranulation and release of preformed mediators, such as histamine, bradykinin, and other vasoactive amines. These inflammatory mediators then give rise to a number of hypersensitivity reactions in the body: vasodilation, increased vascular permeability, mucus secretion, bronchial constriction, sneezing, etc. When this reaction happens against harmless environmental antigens such as pet dander or pollen, it is called an atopic or allergic response. Systemic anaphylaxis is the most severe type I hypersensitivity reaction. Occasionally, mast cell degranulation occurs in an IgE-independent fashion and is called an anaphylactoid response. In this case the mast cell is triggered to degranulate by other mechanisms. This can occur in response to complement anaphylatoxins or contrast iodine. The ultimate host outcome is the same.

Type II (antibody-mediated) hypersensitivity reactions

Type II (antibody-mediated) hypersensitivity reactions are caused by antibodies against specific tissues. In most cases these antibodies are autoantibodies but they can also be produced against a foreign antigen that cross-reacts with self-components of tissues. There are several ways in which host tissue or cellular damage can be caused by this type of reaction. The antibodies may opsonize cells or activate the complement system, recruit neutrophils and macrophages that cause tissue damage, or bind to normal cellular receptors and interfere with their function. A classic example of Type II hypersensitivity is that of hemolytic disease of the newborn. In this disorder Rh-antibody–positive blood leaks across the blood-placental barrier causing the Rh-negative mother to form anti-Rh antibodies. These antibodies, in subsequent pregnancies with Rh-positive fetuses, can cross the placenta and stimulate destruction of red blood cells (RBCs). Other cytotoxic type II reactions include acute rheumatic fever, Goodpasture syndrome, transfusion reactions, and autoimmune thrombocytopenic purport. Noncytotoxic type II reactions include myasthenia gravis, Graves' disease, type II diabetes, and pernicious anemia.

Type III (immune complex) hypersensitivity reactions

Type III (immune complex) hypersensitivity reactions are caused by circulating antibodies (IgG) that complex with antigens. When complexes exceed the ability of the hematopoietic system to phagocytize, the complexes are deposited within the various tissues of the body and activate complement, causing inflammatory response in the tissues. The damage that these reactions cause tends to be systemic, with little tissue or organ specificity. The classic example of type III reactions is that of serum sickness from equine serum used to treat bacterial infections. Other examples of type III disease are systemic lupus erythematosus (SLE), rheumatoid arthritis, or poststreptococcal glomerulonephritis.

Type IV (T-cell-mediated) reactions

Type IV (T-cell-mediated) reactions are characterized by antigen contact with an antigen-sensitized T cell or NK cell. T lymphocytes may cause tissue injury by triggering delayed-type hypersensitivity (DTH) reactions or directly killing target cells. These reactions are elicited by CD4+ TH1 cells and CD8+cells which secrete cytokines that activate macrophages and induce inflammation. These T cells may be autoreactive or specific against foreign protein antigens bound to tissues. There are 3 variants of the type IV reaction: (1) contact hypersensitivity; (2) tuberculin hypersensitivity; and (3) granulomatous hypersensitivity. Contact hypersensitivity causes an eczematous reaction at the point of contact with the antigen. Examples would include reactions to poison ivy, nickel, latex, and chromate. Langerhans cells in the skin participate in recruitment of CD4 cells that ultimately cause cytotoxic damage. In tuberculin hypersensitivity, T cells express cytokines that mediate the inflammatory reaction. In granulomatous hypersensitivity, activated macrophages give rise to epithelioid and giant cell formation. The inflammatory response results in the persistence of microorganisms within macrophages. The pathologic consequences are frequently significant.

Nasal epithelial immunity

The nasal epithelium is constantly engaged in immunomodulation between the host and the environment. Sinonasal epithelial cells have an important role as both mediators

and regulators of innate immune responses and adaptive immune responses in the pathogenesis of AR.[3]

The first line of defense in the nasal epithelium is the mucociliary apparatus, with constant mucociliary clearance of a blanket of mucus containing a variety of antimicrobial products such as immunoglobulins, opsonins, defensins and enzymatic proteins. Ciliary function filters and clears the captured particulate matter in the mucus layer. Impairment of ciliary function leads to stasis of this defense mechanism, as seen in AR and chronic sinus infection.[4,5]

Immune effectors are critical for effective host defense. In addition to local defenses at the mucosal surface, such as mucus and mucociliary transport, the effectors of innate immunity include Toll-like receptors (TLRs), antimicrobial peptides, phagocytic cells, NK cells, and complement. Secreted antimicrobials include defensins, lactoferrin, lysozyme, and the acute phase proteins that serve in chemoattraction and cell activation. They can also immobilize and kill microorganisms. Surfactant proteins SP-A and SP-D are also able to bind and agglutinate bacteria, fungi, and allergens.[3]

TLRs are pattern recognition receptors (PRRs) that recognize pathogen-associated molecular patterns present on a variety of bacteria fungi and viruses. The activation of TLRs induces expression of costimulatory molecules and the release of cytokines that instruct the adaptive immunity. Critical proinflammatory and immunomodulatory cytokines, such as interleukin 1 (IL-1), IL-6, IL-8, IL-10, IL-12, and tumor necrosis factor α (TNF-α) have been are induced after activation of TLR by microbial ligands. Activation of TLRs as part of innate response can influence and modulate the adaptive T-cell response and modify the shaping of the TH1/TH2 balance. TLRs also directly activate host defense mechanisms that combat the foreign invader or contribute to tissue injury. Microbial lipoproteins have the ability to induce both TLR-dependent activation of host defense and tissue pathology. Other antimicrobials include cathelicidins and defensins, which are a broadly dispersed family of antimicrobials against bacteria, fungi, and enveloped viruses.[2,3]

AR

AR is one of the most common chronic diseases, affecting over 500 million people worldwide.[4,5] It has been defined as a symptomatic IgE-mediated hypersensitivity response of the nasal mucosa to allergens. It is characterized by the presence of rhinorrhea, pruritus, sneezing, and nasal congestion/obstruction, postnasal drip, chronic cough, throat clearing, and conjunctivitis.[5] The disease has a significant impact on quality of life and has been shown to affect cognitive functioning, quality of sleep, productivity, examination performance, and psychosocial well-being.[6–8]

AR is comorbid with a variety of other conditions including conjunctivitis, sinusitis, dental malocclusion, and asthma. AR is not only associated with, but is also a risk factor for, the development of asthma.[9–12] Treatment of rhinitis has been shown to improve asthma control.[13–16] In patients who do not have asthma, early and aggressive management of rhinitis may even prevent the development of asthma in later life.[17–19]

AR is by definition an IgE-mediated, type 1 hypersensitivity response of the nasal mucosa to normally innocuous proteins with resultant inflammation.[20] The allergic response is divided into an early and a late phase. In the early phase, antigens initially presented to the nasal mucosa are taken up and processed by APCs into short peptide fragments. These peptide fragments are exteriorized and then recognized by MHC class II molecules. APCs in the draining lymph nodes attract naive CD4+ T cells. In cases of allergic reaction, cytokines including IL-4 are released allowing for polarization and the differentiation of these naive T cells into Th2 cells. Activation of the Th2 response results in the production of IL-4, IL-5, IL-10, and IL-13, which in turn results in the recruitment of IgE-producing B cells, mast cells, and eosinophils.[21,22] Memory B cells maintain this antibody response. IgE molecules bind high-affinity receptors, which "sensitize" the nasal mucosa.[2,22] Re-exposure to the allergen results in crosslinking of adjacent IgE molecules on the surface of both basophils and mast cells. This leads to the degranulation and release of preformed mediators such as histamine and proteases, kinins, and heparin. In addition, prostaglandin 2 (PGD_2) and cysteinyl leukotriene—leukotrienes B_4 (LTB_4), leukotriene C_4 (LTC_4), and leukotriene E_4 (LTE_4)—mediators of the arachidonic acid pathway, are synthesized and secreted by mast cells. These mediators act locally on the surrounding vasculature and nerves located in the nasal mucosa and result in increased vascular permeability, stimulation of glandular secretions, and peripheral vasodilation.[2,23–31] This in turn results in an increase in nasal airway resistance, sneezing, rhinorrhea, and pruritus.[5,30,31] Symptoms generally occur within minutes of exposure.

It has become evident that the nervous system plays an integral role in both the local and distal effects of allergen stimulation through neuronal reflexes.[30–34] Muscarinic receptors are located on the submucosal glands, blood vessels, and on the airway smooth muscle. Inoculation of sensitized antigen to the unilateral nasal septum produces bilateral nasal symptoms, increased glandular markers, in particular lactoferrin, upregulation of eosinophils in the bilateral maxillary sinuses, and ocular symptoms.[30–33] In addition, sensory C nerve fibers are found innervating the walls of muscular arteries, arterioles, venules, venous sinusoids, and glands of both the upper and lower airways. They release a variety of neuropeptides, such as substance P (SP), tachykinin, neurokinin A (NKA), gastrin-releasing peptide, calcitonin gene-related peptide (CGRP), and vasoactive intestinal peptide (VIP), which are believed to augment the allergic inflammatory response.[2,31,35]

Ocular symptoms are a result of a direct allergen reaction on the conjunctival mucosa and nasal ocular reflex responses. This was demonstrated in a double-blind placebo-controlled crossover clinical trial conducted by

Baroody et al.[39] in which allergen was administered topically to the unilateral nasal septum. This not only resulted in increased bilateral nasal symptoms of sneezing, rhinorrhea, and nasal congestion, but ocular symptoms of itching and watery eyes as well. Both nasal and ocular symptoms were reduced by application of topical H1-receptor antagonist to the site of the nasal challenge.

Importantly, the allergic response is not confined to its acute symptoms, 30% to 40% of people will have a delayed or late-phase response (LPR).[5,40–42] The LPR occurs anywhere from 4 to 12 hours after the initial exposure. The most prominent symptom is nasal congestion, with symptoms such as sneezing and rhinorrhea being less robust than in the early phase.[23] This is explained by an increase in the levels of histamine, tonsil-l-arginine methyl ester (TAME)-esterase and to a lesser extent kinins. There is an influx in a variety of inflammatory cells and cellular mediators including Th2 lymphocytes, eosinophils, neutrophils, and basophils, all of which release chemokines and cytokines.[43,44] IL-4, IL-5, and IL-13, along with other inflammatory mediators and chemokines, result in the transendothelial migration and activation of eosinophils.[45–47] IL-5 plays an important role in eosinophil activation and functions to prevent eosinophil apoptosis. Granulocyte macrophage colony-stimulating factor (GM-CSF) is another cytokine associated with eosinophil activation and survival and is increased during both early-phase and late-phase allergic inflammation.[46] The locally produced cytokine "regulated upon activation normal T cell expressed and presumably secreted" (RANTES) is chemotactic for, and involved in, eosinophil activation. RANTES and eotaxin are responsible for transendothelial migration of eosinophils and movement into the epithelium.[47]

In addition, there is endothelial activation with enhanced expression of adhesion molecules, namely intercellular adhesion molecule 1 (ICAM-1) and vascular adhesion molecule 1 (VCAM-1).[48] These cells are important in the local recruitment of inflammatory cells during an allergic response. Late-phase symptoms are most closely correlated with eosinophil levels.[46] Histamine levels correlate more closely with basophil levels, suggesting that basophils and not mast cells are responsible for histamine release in the LPR.[49]

Conclusion

In summary, the innate and adaptive immune systems act in concert to protect us from infectious agents and other harmful substances. Innate immunity responds rapidly on exposure whereas the adaptive immune system is typically slower in activation but provides specific prolonged immunity. AR is a manifestation of a type I hypersensitivity reaction that is mediated by IgE-antibodies and mast cells and is an example of an abnormal adaptive immune system response to normally innocuous proteins with resultant inflammation.

References

1. Murphy KM, Travers P, Walport M. *Janeway's Immunobiology*. Philadelphia, PA: Taylor and Francis; 2007.
2. Baroody FM, Naclerio RM. Immunology of the upper airway and pathophysiology and treatment of allergic rhinitis. In: Flint PW, Haughey BH, Lund VJ, et al., eds. *Cummings Otolaryngology: Head and Neck Surgery*. 5th ed Vol 1. St. Louis, MO: Mobsy; 2010:597–623.
3. Melvin T-A, Ramanathan M. Role of innate immunity in the pathogenesis of allergic rhinitis. *Curr Opin Otolaryngol Head Neck Surg*. 2012;20:194–198.
4. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and Its Impact on Asthma (ARIA) 2008. In collaboration with the World Health Organization, GA^{2}LEN and AllerGen. *Allergy*. 2008;63(Suppl 86): 8–160.
5. Bousquet J, Van Cauwenberge P, Khaltaev N; Aria Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol*. 2001;108(5 Suppl):S147–S334.
6. Wilken JA, Berkowitz R, Kane R. Decrements in vigilance and cognitive functioning associated with ragweed-induced allergic rhinitis. *Ann Allergy Asthma Immunol*. 2002;4:372–380.
7. Ferguson BJ. Influences of allergic rhinitis on sleep. *Otolaryngol Head Neck Surg*. 2004;130:617–629.
8. Bhattacharyya N. Incremental healthcare utilization and expenditures for allergic rhinitis in the United States. *Laryngoscope*. 2011;121:1830–1833.
9. Corren J. Allergic rhinitis and asthma: how important is the link? *J Allergy Clin Immunol*. 1997;99:S781-S786.
10. Guerra S, Sherrill DL, Martinez FD, et al. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol*. 2002;109:419–425.
11. Settipane RJ, Hagy GY, Settipane GA. Long-term risk factors for developing asthma and allergic rhinitis: a 23-year follow-up of college students. *Allergy Proc*. 1994;15:21–25.
12. Leynaert B, Bousquet J, Neukirch C, Liar R, Neukirch F. Perennial rhinitis: an independent risk factor for asthma in nonatopic subjects: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol*. 1999;104:301–304.
13. Jones C, Holt P. Immunopathology of allergy and asthma in childhood. *Am J Respir Crit Care Med*. 2000;162:S36-S39.
14. Stelmach R, do Patrocinio T, Nunes M, et al. Effect of treating allergic rhinitis with corticosteroids in patients with mild-to-moderate persistent asthma. *Chest*. 2005;128:3140–3147.
15. Watson WT, Becker AB, Simons FE. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway responsiveness. *J Allergy Clin Immunol*. 1993;91:97–101.
16. Jani A, Hamilos D. Current thinking on the relationship between rhinosinusitis and asthma. *J Asthma*. 2005;42:1–7.
17. Möller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT study). *J Allergy Clin Immunol*. 2002;109:251–256.
18. Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children—a 14 year study. *Pediatrics*. 1968;42:793–802.
19. Jacobsen L, Nūchel PB, Wihl HA, Løwenstein H, Ipsen H. Immunotherapy with partially purified and standardized tree pollen extracts. IV: Results from long-term (6 year) follow-up. *Allergy*. 1997;52:914–920.
20. Çobanoğlu B, Toskala E, Ural A, Cingi C. Role of leukotriene antagonists and antihistamines in the treatment of allergic rhinitis. *Curr Allergy Asthma Rep*. 2013;13:203–208.
21. Romagnani S. The Th1/Th2 paradigm. *Immunol Today*. 1997;18:263–266.
22. Maggi E. The TH1/TH2 paradigm in allergy. *Immunotechnology*. 1997;3:233–244.
23. Bousquet J, Vignola AM, Campbell AM, Michel FB. Pathophysiology of the allergic response. *Int Arch Allergy Immunol*. 1996;110:207–218.
24. Castells M, Schwartz LB. Tryptase levels in nasal-lavage fluid as an indicator of the immediate allergic response. *J Allergy Clin Immunol*. 1988;82:348–355.
25. White MV, Kaliner MA. Mediators of allergic rhinitis. *J Allergy Clin Immunol*. 1992;90:699–704.
26. Baumgarten CR, Togias AG, Naclerio RM, Lichtenstein LM, Norman PS, Proud D. Influx of kininogens into nasal secretions following antigen challenge of allergic individuals. *J Clin Invest*. 1985;76:191–197.
27. Creticos PS, Peters SP, Adkinson NF Jr, et al. Peptide leukotriene release after antigen challenge in patients sensitive to ragweed. *N Engl J Med*. 1984;310:1626–1630.
28. Bascom R, Pipkorn U, Proud D, et al. Major basic protein and eosinophil-derived neurotoxin concentrations in nasal lavage fluid after antigen challenge: effect of systemic corticosteroids and relationship to eosinophil influx. *J Allergy Clin Immunol*. 1989;84:338–346.
29. Sin Min-Ho, Averill FJ, Hubbard WC et al. Nasal allergen challenge generates 1-0-hexadecyl-2-lyso-sn-glycero-3-phosphocholine. *Am J Respir Crit Care Med*. 1994;149(3 Pt 1):660–666.
30. Wagenmann M, Baroody FM, Desrosiers M, et al. Unilateral nasal allergen challenge leads to bilateral release of prostaglandin D2. *Clin Exp Allergy*. 1996;26:371–378.
31. Raphael GD, Igarashi Y, White MV, Kaliner MA. The pathophysiology of rhinitis: V. Sources of protein in allergen-induced nasal secretions. *J Allergy Clin Immunol*. 1991;88:33–42.

32. Baroody FM, Ford S, Lichtenstein LM, Kagey-Sobotka A, Naclerio RM. Physiologic responses and histamine release after nasal antigen challenge: effect of atropine. *Am J Respir Crit Care Med*. 1994;149:1457–1465.
33. Baroody FM, deTineo M, Naclerio RM. Unilateral nasal allergic reactions increase bilateral sinus eosinophil infiltration. *J Applied Physiol*. 2013;115:1262–1267.
34. Canning BJ. Reflex regulation of airway smooth muscle tone. *J Applied Physiol*. 2006;101:971–985.
35. Baraniuk JN, Lundgren JD, Goff J, et al. Calcitonin gene-related peptide in human nasal mucosa. *Am J Physiol*. 1990;258:L81–L88.
36. Baraniuk JN, Lundgren JD, Okayama M, et al. Substance P and neurokinin A in human nasal mucosa. *Am J Respir Cell Mol Biol*. 1991;4:228–236.
37. Schierhorn K, Brunnée T, Schultz KD, Jahnke V, Kunkel G. Substance-P-induced histamine release from human nasal mucosa in vitro. *Int Arch Allergy Immunol*. 1995;107:109–114.
38. Mosimann BL, White MV, Hohman RJ, Goldrich MS, Kaulbach HC, Kaliner MA. Substance P, calcitonin gene-related peptide, and vasoactive intestinal peptide increase in nasal secretions after allergen challenge in atopic patients. *J Allergy Clin Immunol*. 1993;92:95–104.
39. Baroody FM, Foster K, Markarian A, deTineo M, Naclerio RM. Nasal ocular reflexes and eye symptoms in patients with allergic rhinitis. *Ann Allergy Asthma Immunol*. 2008;100:194–199.
40. Naclerio RM, Proud D, Togias AG, Adkinson N, et al. Inflammatory mediators in late antigen induced rhinitis. *N Engl J Med*. 1985;313:65–70.
41. Dvoracek JE, Yunginer JW, Kern EB, Hyatt RE, Gleich GJ. Induction of nasal late-phase reactions by insufflation of ragweed-pollen extract. *J Allergy Clin Immunol*. 1984;73:363–368.
42. Taylor G, Shivalkar PR. "Arthus type" reactivity in the nasal airways and skin in pollen sensitive subjects. *Clin Allergy*. 1971;1:407–414.
43. Bentley AM, Jacobson MR, Cumberworth V, et al. Immunohistology of the nasal mucosa in seasonal allergic rhinitis: increases in activated eosinophils and epithelial mast cells. *J Allergy Clin Immunol*. 1992;89:877–883.
44. Pastorello EA, Galeazzo G, Riario-Sforza MD, Segala M, Fumagalli M, Gandini R. Comparison of rhinomanometry, symptom score and inflammatory cell counts in assessing the nasal late-phase reaction to allergen challenge. *J Allergy Clin Immunol*. 1994;93:85–92.
45. Masuyama K, Jacobson MR, Rak S, et al. Topical glucocorticosteroid (fluticasone propionate) inhibits cells expressing cytokine mRNA for interleukin-4 in the nasal mucosa in allergen-induced rhinitis. *Immunology*. 1994;82:192–199.
46. Nouri-Aria KT, Masuyama K, Jacobson MR, et al. Granulocyte/macrophage-colony stimulating factor in allergen-induced rhinitis: cellular localization relation to tissue eosinophilia and influence of topical corticosteroid. *Int Arch Allergy Immunol*. 1998;117:248–254.
47. Alam R, Stafford RA, Forsythe P, et al. RANTES is a chemotactic and activating factor for human eosinophils. *J Immunol*. 1993;150:3442–3448.
48. Montefort S, Feather IH, Wilson SJ, et al. The expression of leukocyte-endothelial adhesion molecules is increased in perennial allergic rhinitis. *Am J Respir Cell Mol Biol*. 1992;7:393–398.
49. Bascom R, Wachs M, Naclerio RM, Pipkorn U, Galli SJ, Lichtenstein LM. Basophil influx occurs after nasal antigen challenge: effects of topical corticosteroid pretreatment. *J Allergy Clin Immunol*. 1988;81:580–589.