

Gastrointestinal immunopathology and food allergy

Joseph A. Bellanti, MD*; Aderbal Sabra, MD, PhD*†; and Barbara J. Zeligs, BS*

Objective: To review the current data that support the pivotal function of the gastrointestinal immune system in health and disease and its critical role in the pathogenesis of a wide variety of clinical disorders associated with food allergy (FA).

Data Sources: Internet-based literature search and our own data.

Study Selection: The studies included in this review were selected based on the expert opinion of the authors.

Results: In contrast to the beneficial expressions of gastrointestinal-associated lymphoid tissue, which are seen with relevance to newer methods of delivery of vaccines directly applied to the gastrointestinal mucosal surfaces (eg, oral poliovirus, rotavirus, *Salmonella typhi* vaccines), the adverse consequences of a mucosal immune response gone astray are evidenced in many diseases such as FA. A classification of clinical disorders associated with FA based on classic mechanisms of immunologic injury is presented, which includes the following: (1) IgE-mediated, (2) non-IgE-mediated, and (3) mixed IgE- and non-IgE-mediated disorders. Our study of immunologic disturbance in patients with non-IgE FA revealed a pattern of increased CD4⁺ and decreased T_H1 cell counts in peripheral blood mononuclear cells in contrast to patients with celiac disease, where a pattern of increased CD8⁺ and T_H1 cell counts in peripheral blood mononuclear cells and increased CD8⁺ cell counts was seen.

Conclusions: The gastrointestinal immune response thus plays a pivotal role in maintaining protective immunity in health and a critical role in the pathogenesis of a wide variety of clinical disorders associated with FA.

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INTRODUCTION

It has become increasingly apparent that the gastrointestinal tract not only serves a nutritive function but also is a major immunologic organ. Within the lifespan of an individual, it interacts with innumerable constituents, most of which are food proteins, peptides, and microorganisms. The gastrointestinal immune system, therefore, has the important obligatory dual function of selecting nutrients essential for cellular growth and simultaneously promoting beneficial responses to microbes and avoiding immunologic errors to food proteins, which could lead to the manifestations of food allergy (FA). In this article, we review data that support the pivotal function of the gastrointestinal immune system in health and disease and its critical role in the pathogenesis of a wide variety of clinical disorders associated with FA. The studies included in this review were selected from the authors' own articles and those obtained from a PubMed literature search and chosen based on the authors' expert opinion.

MUCOSA-ASSOCIATED LYMPHOID TISSUES: ANATOMIC ORGANIZATION

It is now generally recognized that there exists in the human a highly integrated and finely regulated common mucosal immune system referred to as the mucosa-associated lymphoid tissue (MALT), which consist of an extensive network of cells and cell products found on the vast domain of mucosal surfaces that interface with the external environment and that protect us from entry of foreign substances.¹ Although originally conceived of as a local immune system only found at body surfaces, separate and distinct from a peripheral immune system, it is now clear that MALT is only one component of a broader unified immune system.

Immunologically activated T and B lymphocytes derived from the generalized lymphatic drainage are comingled in the lymph node with counterpart T and B lymphocytes derived from stimulation at mucosal and skin sites and enter the blood through the thoracic duct (Fig 1). From there, this collection of lymphocytes forms a recirculating pool that can "home" back to their original mucosal sites of sensitization or to other mucosal sites. This recirculating pool of sensitized T and B lymphocytes in the blood can also percolate back into the lymph node in primary lymphoid tissues and other secondary lymphoid tissues at mucosal sites through unique structures called *postcapillary venules*.² Thus, lymphocytes enter the lymph node through both the vascular and lymphatic channels and form a continuously recirculating pool of lympho-

* Departments of Pediatrics and Microbiology-Immunology and the International Center for Interdisciplinary Studies of Immunology, Georgetown University Medical Center, Washington, DC.

† The Department of Pediatric Gastroenterology, Universidade do Grande Rio, Rio de Janeiro, Brazil.

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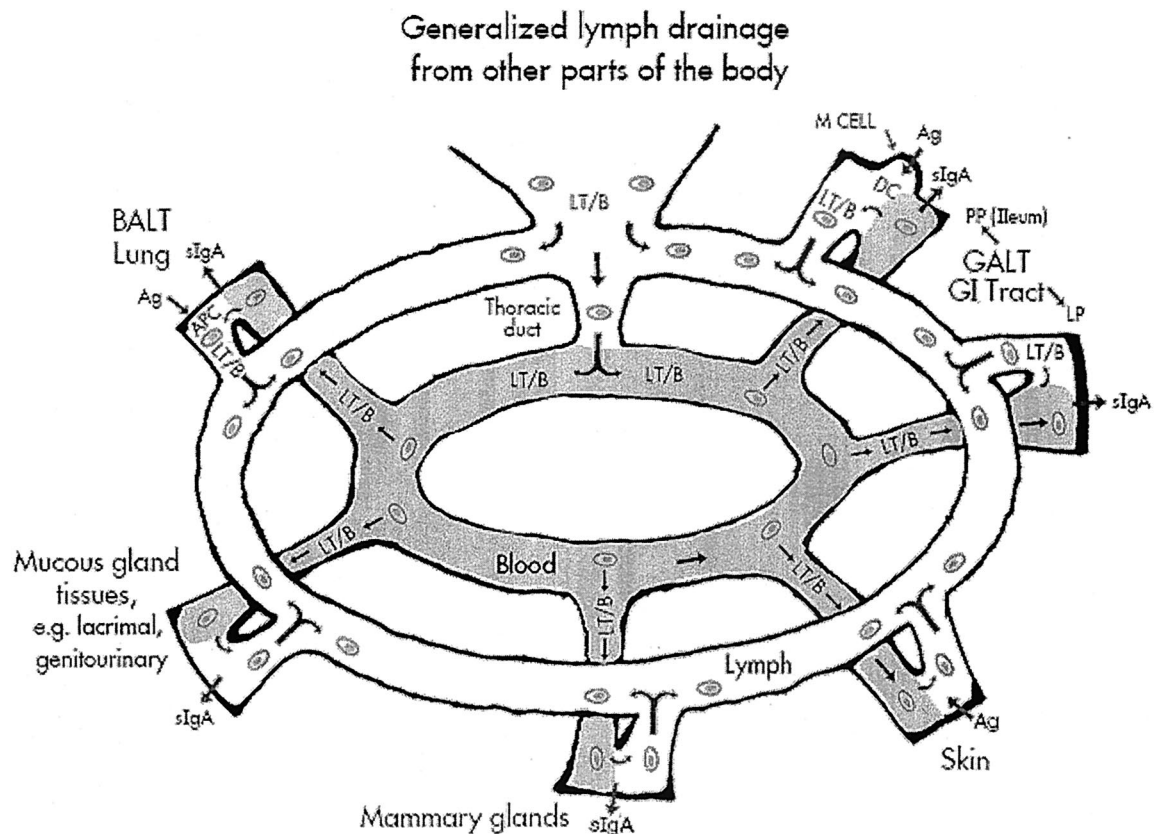


Figure 1. Unique features of the mucosa-associated lymphoid tissue (MALT) and its relationship to the total immunologic system. Ag indicates antigen; APC, antigen-presenting cell; BALT, bronchus-associated lymphoid tissue; DC, dendritic cell; GALT, gastrointestinal-associated lymphoid tissue; GI, gastrointestinal; LP, lamina propria; LT/B, T and B lymphocytes; PP, Peyer patch; sIgA, secretory IgA.

cytes prepared to function at internal sites and mucosal surfaces.

Included within MALT are the mucosal surfaces of the gastrointestinal, respiratory, and genitourinary systems and all tissues that interface with the external environment (Fig 1). For ease of discussion, the various components of MALT have been classified into clusters of anatomically organized sites (Table 1 and Fig 1), which include (1) the gut-associated lymphoid tissues (GALT), (2) the skin-associated lymphoid tissues, (3) the mammary-associated lymphoid tissues, (4) other mucous gland-secreting tissues (eg, lacrimal, genitouri-

nary systems), and (5) the bronchus-associated lymphoid tissues (BALT) and the nasopharyngeal-associated lymphoid tissues.³

MUCOSAL IMMUNE SYSTEM: INDUCTIVE SITES AND EFFECTOR SITES

At each mucosal site of MALT, there are 2 important immunologic components: (1) inductive sites, those secondary lymphoid tissues that facilitate antigen uptake, processing, and presentation; and (2) effector sites, those more diffuse anatomic tissue locations where antigen-specific T and B

Table 1. Major Inductive Tissues and Examples of Clinical Involvement in MALT

Anatomic site	Major inductive tissues	Example of clinical involvement
Gut-associated lymphoid tissues	Jejunum (PP), ileum (M cells)	Celiac disease, food allergy
Skin-associated lymphoid tissues	Dermal lymphoid tissue	Atopic eczema
Mammary-associated lymphoid tissues	Mammary lymphoid tissues	Protective immunity for newborn
Mucous gland tissues	Lacrimal lymphoid tissues	Allergic conjunctivitis
	Genitourinary tissues	Protective immunity
Bronchus-associated lymphoid tissues	Peribronchial lymphoid tissue	Asthma
Nasopharyngeal-associated lymphoid tissues	Palatine tonsils and adenoids	Allergic rhinitis

Abbreviations: MALT, mucosa-associated lymphoid tissue; PP, Peyer patches.

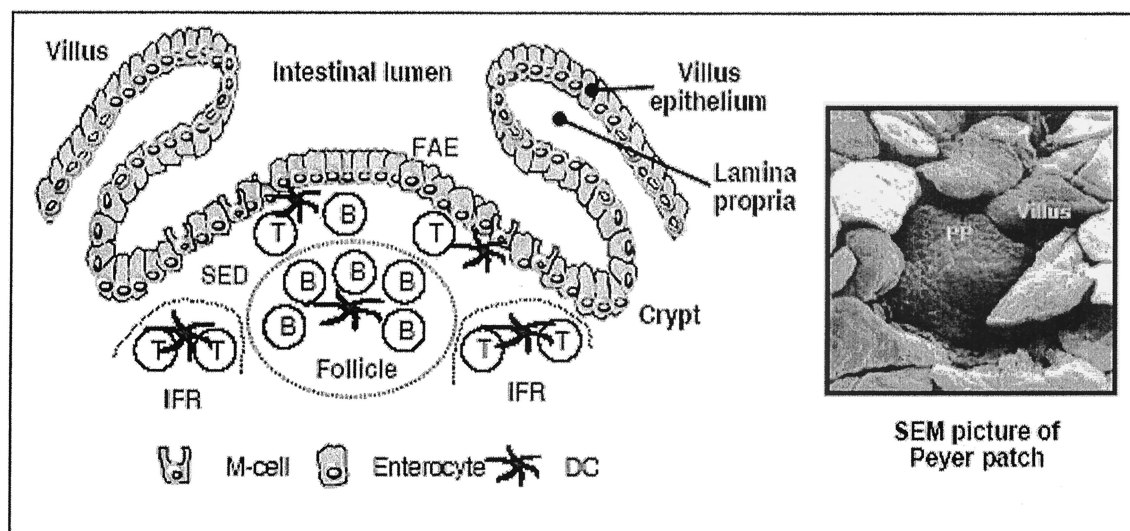


Figure 2. Anatomic structures associated with the induction of an immune response in a Peyer patch (PP) in the lower small intestine. The follicle-associated epithelium (FAE) covers the dome of the PP and transport of macromolecular antigen occurs across the surface epithelium through M cells. In the subepithelium dome (SED) region and interfollicular region (IFR), dendritic cells that interact with T and B lymphocytes (T and B) are found. On the right of the figure is a scanning electron micrograph (SEM) of a PP.

cells ultimately reside and perform their respective functions to protect mucosal surfaces or give rise to disease.¹ After initial exposure to antigen at inductive sites in MALT, mucosal lymphocytes leave the inductive site and home to mucosal effector tissues.

With evolution, the mammalian host has developed organized secondary lymphoid tissues in the upper respiratory and gastrointestinal tract regions that facilitate antigen uptake, processing, and presentation for induction of mucosal immune responses. The major inductive tissues involved in MALT and examples of clinical involvement are given in Table 1. The GALT are divisible into 2 types of inductive sites: (1) the lymphoid tissues in the lower small intestine (ie, the ileum), which are organized in the Peyer patches (PP), and (2) the remainder of the small intestinal immune system, which is organized within the intestinal villi in the lamina propria into secondary lymphoid tissues primarily in the upper gastrointestinal tract (Fig 1).⁴ Effector sites for mucosal immune responses include the lymphoid cells in the lamina propria (ie, lamina propria lymphocytes) regions of the gastrointestinal, upper respiratory, and reproductive tracts and secretory glandular tissues, such as mammary, salivary, and lacrimal glands.

After entry of a protein at any of these mucosal sites, the intact protein or its peptides are absorbed across the mucosal barrier, where they interact with T and B lymphocytes either directly or through the collaboration of antigen-presenting cells (APCs), which in the gastrointestinal tract take the form of macrophages, dendritic cells, or specialized microvillous epithelial cells (M cells)⁵ (Fig 2). The cellular participants of these interactions will determine whether these proteins or peptides will be recognized and processed with a resultant

immune response or with immunologic unresponsiveness referred to as immunologic tolerance.⁶ Both outcomes involve an active set of immunologic processes in which T-cell recognition of antigen is pivotal and requires a trimolecular complex interaction of the T-cell receptor (TCR), antigenic peptides, and the major histocompatibility complex (MHC) molecules (class I and II). T-cell recognition of antigen requires that peptides derived from the proteins be displayed within the cleft of a MHC molecule on the membrane of a cell. To mediate these responses, the immune system uses 2 different antigen-presenting pathways: (1) the exogenous pathway in which exogenous antigens are processed in the endocytic pathway and presented to T cells on the membrane of the APCs with class II MHC molecules and (2) the endogenous pathway in which endogenous antigens are processed in the cytosolic pathway and presented in the membrane of a target cell with a class I MHC molecule. The TCR dictates the antigenic specificity of the response and plays a central role in initiating activation of the target cell, with its MHC I-associated peptide or inactivation of the APCs through its MHC II-associated peptide. To generate a complete immune response, T cells require 2 distinct signals for activation and subsequent proliferation into effectors cells: (1) an initial signal (signal 1), which is generated by an interaction of TCR-CD3 complex, and (2) a costimulatory signal (signal 2), which is provided by interaction between CD28 on the T cell and members of the B7 family on the APCs.⁷

Most of the proteins absorbed from the small intestine are presented to the T and B lymphocytes and are mediated by MHC class II in the absence of dendritic cells. In this scenario, with the absence of the costimulatory signal, signaling

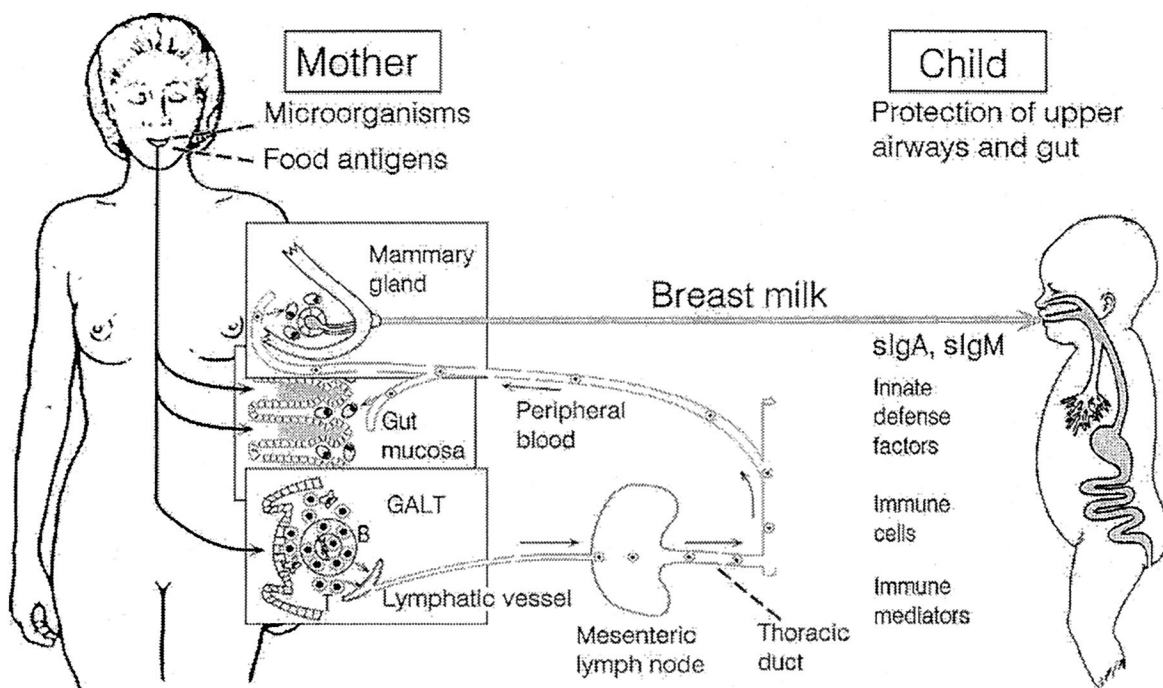


Figure 3. Integration of mucosal immunity between the mother and newborn, showing the linkage of the mucosal immunologic systems of the mother and child. After initial sensitization to the food antigens and microflora found in the gastrointestinal tract of the mother, primed B and T lymphocytes from Peyer patches leave via lymph and peripheral blood to the lactating mammary gland, where local production of secretory antibodies (sIgA and sIgM) specific for enteric antigens (microorganisms and food proteins) occurs. Reproduced with permission from Brandtzaeg.¹⁷

would be inhibitory and the activation of the T cell is down-regulated. This would result in a silencing of the immunologic response to the ingested protein (ie, immunologic tolerance) induced by CD8 suppressor lymphocytes or, as described recently, by a third subset of lymphocytes referred to as T_H3 regulatory cells.⁸ However, if proteins that escape digestion reach the terminal ileum and are processed by the M cell through the dendritic cell, the T cell will receive 2 distinct signals for activation through the MHC II system, resulting in a complete immune response with immune activation. At this point, the T and B cells in the lower small intestine (ie, the ileum) are activated in the PP and are prepared to travel across lymphoid follicles into the lymphatic system and then into the general circulation.⁹

The PP contain a dome beneath which are found lymphoid follicles (B-cell zones with germinal centers) and interfollicular regions enriched with T cells (Fig 2). The upper surface of the dome is covered by a specialized follicle-associated epithelium, 10% to 20% of which is composed of microvilli or M cells that exhibit thin extensions around the lymphoreticular cells.¹⁰⁻¹³ These extensions, which interact with B and T lymphocytes and occasional macrophages and dendritic cells, form an immunologic unit.¹¹⁻¹³ The M cells, which function as APCs, are uniquely specialized for uptake and transport of luminal antigens, including proteins and particulates such as microorganisms.^{10,11}

MUCOSAL IMMUNE SYSTEM: HOMING

Following sensitization at mucosal sites, the activated T and B lymphocytes then migrate to any of the several specific target organs that comprise MALT by a process referred to as homing.¹⁴ The precise mechanism(s) for homing is not fully understood but appears to be related to a selective tropism of the activated lymphocytes for a given target organ, a selectivity that is genetically unique to each allergic individual and that is achieved by selective adhesion molecules¹⁵ that direct the T and B lymphocytes to a selected organ. Although homing can occur at any component part of MALT, it appears that primed immune cells preferentially home to effector sites that correspond to the inductive sites where they initially responded to antigens.

At a given homing site, the B and T cells on subsequent encounter of an offending food antigen will be immunologically activated with the release of products (eg, antibody, cytokines, and vasoactive peptides), which would give rise to an inflammatory reaction in the affected organ responsible for clinical manifestations of allergy in an affected individual. For example, an infant sensitized to cow's milk protein through the oral ingestion of cow's milk, whose T and B lymphocytes home to the skin, would react with atopic dermatitis known to occur after subsequent ingestion at the site of an immunologic reaction of cow's milk. Another infant

similarly sensitized to cow's milk and whose sensitized T and B lymphocytes have homed to the bronchial tree would react with obstructive manifestations characteristic of bronchial asthma.¹⁶

ENTEROMAMMARY CIRCULATION

Lactating mammary glands are yet another part of the mucosal immune system and in the human participate in a set of remarkable immunologic events, which link the inductive sites of the GALT, BALT, and mammary-associated lymphoid tissues of the mother with the effector sites of the gut and upper airways of the breast-fed infant¹⁷ (Fig 3). After initial sensitization to food antigens or microflora found in the GALT and BALT of the mother, primed B and T lymphocytes from PP or peribronchial lymphoid tissues leave these sites via the lymph nodes and peripheral blood and home to the lactating mammary gland, where local production of secretory antibodies (sIgA and sIgM) specific for these antigens occurs. Breast milk, therefore, contains a boutique of specialized antibodies that result from antigenic stimulation in the inductive sites of MALT in both the gut and airways of the mother. This has been documented by showing that sIgA from breast milk exhibits antibody specificity for a wide range of common intestinal and respiratory pathogens.¹⁸ The secretory antibodies are thus highly targeted against infectious agents in the mother's environment, which are those likely to be encountered by the infant during his or her first weeks of life. In addition to its role in infectious disease, the benefits of breast-feeding in the prevention of allergic disease in the infant are well documented.¹⁹ Thus, breast-feeding represents a unique immunological integration of the mucosal immunologic systems of the mother and child, which has biologic significance both in the protection afforded the breast-fed infant against infectious disease and in the prevention of allergic disease.^{19,20}

MUCOSAL IMMUNE SYSTEM: BENEFICIAL EXPRESSIONS OF MUCOSAL IMMUNIZATION

In recent years, the need to identify alternative routes of immunization for the prevention of infectious diseases has received increasing attention.²¹ Among the newer methods of vaccine delivery is mucosal immunization or the direct application of the vaccine to mucosal surfaces of the common mucosal immune system. Perhaps the first good example of this type of immunization was the development and use of the oral poliovirus vaccine developed by Sabin,²² where attenuated vaccine strains of poliovirus are administered via the oral route, the natural portal of entry of the wild-type virus. Other vaccines developed for application to the gastrointestinal mucosal immune system is the live attenuated *Salmonella typhi* vaccine²³ and the rotavirus vaccine.²⁴ In a similar fashion, influenza²⁵ and measles²⁶ viral vaccines more recently have been adapted for delivery to the respiratory tract by aerosol or nasal spray. The use of the mucosal route of immunization offers distinct advantages over the parenteral route not only of simplicity and avoidance of the needle and syringe but also in producing both mucosal and systemic immunity. This represents a continuing area of development of many future vaccines.

MUCOSAL IMMUNE SYSTEM: HARMFUL EXPRESSIONS IN FA

The adverse consequences of a mucosal immune response are seen in disorders where the outcome of the immune response is not beneficial, as in the case of FA. Table 2 lists the clinical disorders associated with FA according to specific MALT systems and affected target organs.²⁷ For ease of discussion, it may be possible to divide the clinical disorders into 3 categories according to postulated immunologic mechanisms: (1) the IgE-mediated disorders, (2) the non-IgE-mediated disorders, and (3) the mixed IgE and non-IgE disorders.

Table 2. Clinical Disorders Associated with Food Allergy According to Specific MALT System and Affected Target Organ

Immunologic mechanism	Affected MALT system	Target organ	Clinical disorder
IgE	GALT	GI tract	Immediate GI hypersensitivity, oral allergy syndrome
	SALT	Skin	Acute urticaria, angioedema
	BALT	Respiratory tract	Bronchospasm, asthma, anaphylaxis
	NALT		Rhinitis
Non-IgE	GALT	GI tract	Celiac disease, cow's milk enteropathy, dietary protein enterocolitis, breast milk colitis, proctocolitis, proctitis
	SALT	Skin	Dermatitis herpetiformis
	BALT	Respiratory tract	Heiner syndrome
Mixed IgE and non-IgE	GALT	GI tract	Eosinophilic esophagitis, eosinophilic gastroenteritis
	SALT	Skin	Atopic dermatitis
	BALT	Respiratory tract	Food allergy-induced bronchial asthma

Abbreviations: BALT, bronchus-associated lymphoid tissue; GALT, gut-associated lymphoid tissue; GI, gastrointestinal; NALT, nasopharyngeal-associated lymphoid tissue; MALT, mucosa-associated lymphoid tissue; SALT, skin-associated lymphoid tissue.

NON-IgE-MEDIATED FA

Although much progress has made in the field of IgE-mediated FA, recent studies suggest a role for non-IgE-mediated FA and an imbalance of T_H1/T_H2 lymphocytes in the pathogenesis of FA. The presence of a mucosal intestinal lesion of ileal lymphonodular hyperplasia has been found in a variety of inflammatory bowel diseases of the gastrointestinal tract and FA.²⁸ We recently published our findings of T_H1 and T_H2 cytokines profiles in patients with FA and celiac disease.²⁹

In our study,²⁸ we observed a pattern of immunologic disturbance in patients with non-IgE FA with increased $CD4^+$ cell counts and decreased T_H1 cell counts in peripheral blood mononuclear cells and ileal lymphonodular hyperplasia. In contrast, in patients with celiac disease, a pattern of increased $CD8^+$ and T_H1 cell counts in peripheral blood mononuclear cells and increased $CD8^+$ cell counts was seen in jejunal tissue. Kokkonen and Karttunen²⁹ have studied lymphonodular hyperplasia in various gastrointestinal tract sites and view lymphonodular hyperplasia as a marker of enhanced immune response. Our findings of T_H1 dysfunction and ileal lymphonodular hyperplasia in patients with non-IgE FA are consistent with this concept and provide the first strong data to support an immunologic basis for non-IgE-mediated FA and suggest a possible new relationship between T_H1 dysfunction and the gastrointestinal lesion of ileal lymphonodular hyperplasia. The results of these studies not only lend further support for the relationship of T_H1/T_H2 imbalance and allergic diseases but also provide a basis for better understanding of the pathogenesis of non-IgE FA and celiac disease. They also suggest the need for further study of the role of the gastrointestinal immune system in the pathogenesis of other immunologically mediated disorders of other organ systems.

CONCLUSIONS

It has become increasingly apparent that the gastrointestinal tract not only serves a nutritive function but also is a major immunologic organ that is part of a highly integrated and finely regulated common mucosal immune system referred to as MALT. MALT consists of an extensive network of cells and cell products found on the vast domain of mucosal surfaces that interface with the external environment and function to exclude the penetration of foreign and potentially inimical substances from entry into the internal milieu. Innocuous dietary food proteins and components of commensal bacteria in the normal gastrointestinal tract activate suppressive mechanisms collectively called *oral tolerance*, which provide an explanation for the lack of adverse immune reactions to persistent contact with these harmless environmental and dietary proteins. The gastrointestinal immune system, therefore, has the important obligatory dual function of selecting nutrients essential for cellular growth and simultaneously avoiding immunologic errors to food proteins, which may take the form of FA. The goal of this system is protective immunity, and recent advances in vaccine development have used the mucosal immune system to provide alternate and improved vaccines for mucosal immunization for the preven-

tion of infectious diseases. However, like the systemic immune system, the mucosal immune system is susceptible to aberrations of immunologic function, including immune deficiency, allergy, hypersensitivity, and inflammation. The mucosal immune system is unique in that it can provide both positive and negative signals for the induction and regulation of immune responses in both mucosal and systemic compartments after mucosal antigen exposure. Communication among the various parts of MALT is important for initial sensitization at inductive sites and homing of lymphocytes to target organs at effector sites. This homing is performed by adhesion molecules that recognize mucosal addressins expressed on high endothelial venule cells and is the major pathway by which the mucosal immune system connects the diverse compartments located in the gastrointestinal, pulmonary, and genitourinary tracts and exocrine glands. Such unique properties distinguish the mucosal from the systemic immune system. In contrast to mucosal immunization, the induction of peripheral immune responses by parenteral antigen does not result in significant mucosal immunity. However, mucosal immunization (eg, oral or nasal administration of antigen) can induce antigen-specific immune responses in distant mucosa-associated tissues. The gastrointestinal immune response thus plays a pivotal role in maintaining protective immunity in health and in the pathogenesis of a wide variety of clinical disorders associated with FA.

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Requests for reprints should be addressed to:
Joseph A. Bellanti, MD
Georgetown University Medical Center
3800 Reservoir Rd NW
Washington, DC 20007
E-mail: bellantj@georgetown.edu