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Allergology International

journal homepage: <http://www.elsevier.com/locate/alit>

Editorial

New trends in mucosal immunology and allergy

In *Allergology International* (AI) Vol. 68, Issue 1, we feature a set of review articles entitled “New Trends in Mucosal Immunology and Allergy” as well as original articles and letters to the editor. We believe that this issue will greatly contribute to our readers' understanding of the current concepts of mucosal immunology and its relation to the induction and regulation of allergic diseases.

The human body possesses multiple tube-like structures lined with mucosae, representing the largest surface area in the body. These include the oral and nasal cavities, respiratory and digestive tracts, ocular cavity, ear cavity, and genitourinary tract, together forming the interactive platform between the inner and outer environments. Because of its large surface area and continuous exposure to the outside environment, the mucosa of the aero-digestive tract is the major admittance route of most undesired antigens, such as allergens and pathogens, via inhalation and ingestion.^{1–3} The host is equipped with a dynamic and flexible immunological barrier, known as the mucosal immune system, to distinguish between beneficial and harmful antigens, thus providing two distinct immunological conditions of symbiosis and elimination.¹ The mucosa of the aero-digestive tract has essential roles in the daily physiological functions of inhalation and ingestion and is integral to these basic life-supporting systems. These synchronized yet distinct biological roles—immunological as well as physiological machineries—are unique characteristics of the mucosae of the airway and digestive tracts.

To provide a protective barrier at the mucosal surfaces, the innate and acquired immune systems need to operate harmoniously. Physical and chemical barriers—consisting of tight junctions and a dense layer of mucins, including antimicrobial peptides^{1,4}—are crucial elements in the first line of defense,^{1–5} together with components of innate immunity, including Toll-like receptors^{6–8} and innate immune cells (e.g., innate lymphoid cells, natural killer cells, natural killer T cells, mast cells, and eosinophils).^{9–12} Integral to acquired immunity at the mucosal epithelium of the aero-digestive tract, secretory IgA (SIgA) antibodies are key humoral factors in preventing the entrance of unwanted pathogenic and allergic antigens.^{13–15} In addition, these IgA antibodies are involved in creating symbiotic conditions for the commensal microbiota, thus contributing to the creation and maintenance of mucosal homeostasis in the harsh environment of the aero-digestive tract.¹⁶ Although the SIgA system plays a critical immunological role in establishing commensalisms and exclusionism against beneficial and detrimental antigens, respectively, it

is still not clear whether allergen-specific SIgA antibodies are beneficial in allergic diseases. In this regard, recent studies have suggested that allergen-specific SIgA antibodies induced in the aero-digestive tract limit the worsening of allergic inflammation.^{17,18}

In order to induce antigen-specific SIgA antibodies, antigens must be delivered directly to the mucosal epithelium of the aero-digestive tract—especially its inductive component of mucosa-associated lymphoid tissue (MALT), equipped with professional antigen-sampling M cells, and antigen-presenting cells (e.g., dendritic cells) for initiating antigen-specific immune responses.^{5,19–22} Oral and nasal delivery of an optimal dose of antigens incorporated in the appropriate targeting and delivery vehicle to gut-associated lymphoid tissue (GALT) and nasopharynx-associated lymphoid tissue (NALT) leads to the generation of antigen-specific SIgA antibodies in the secretions of the gastrointestinal and upper respiratory tracts. Further, these mucosal administration routes effectively stimulate the systemic immune responses, including the induction of serum IgG antibodies. At the same time, mucosal administration of large doses of antigen and/or prolonged antigen mucosal delivery induces systemic unresponsiveness to protein antigen, an immunological suppression status (e.g., oral tolerance).²³ These facts indicate that the concept of the mucosal immune system can be adopted for new-generation vaccines rationally designed to efficiently elicit both allergen-specific mucosal immunity at the entry sites of aero-digestive allergic agents and, simultaneously, allergen-specific systemic unresponsiveness for the control of allergic diseases.

We need to know more about the uniqueness of the mucosal immune system to better understand its relation to allergy development. This will help in adapting to the next generation of mucosal immunotherapy and of vaccines for the prevention and control of allergic diseases. It is critical to create an immunologically rational scientific platform for the contributions of two major immunological arms of innate (e.g., innate lymphoid cells) and acquired (e.g., SIgA and oral tolerance) immunity against allergens at the mucosal epithelium of the respiratory and digestive tracts. To this end, this issue of *Allergology International* features three inter-related review articles summarizing the roles of innate lymphoid cells and their related cytokines (e.g., IL-22) for the induction and regulation of allergic responses in the airways. The articles include the roles of the gut mucosal immune network in mediating a fine-tuned immunological balance between active (e.g., undesired antigen-specific SIgA) and quiescent (e.g., oral tolerance to beneficial antigens),^{24–26} thus maintaining intestinal healthy homeostasis, including the control of allergic responses. Ito and his colleagues have nicely discussed recent progress in our

Peer review under responsibility of Japanese Society of Allergy.

<https://doi.org/10.1016/j.alit.2018.12.002>

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understanding of the biological aspect of IL-22 as well as its bidirectional role in the induction and regulation of airway allergic inflammation.²⁴ Doherty and Broide have introduced and extensively discussed newly identified innate lymphoid cells (ILC), focusing on type 2 ILC (or ILC2) in asthma and respiratory allergic diseases, by using both human and experimental animal systems.²⁵ Finally, Tokuhara and his colleagues have comprehensively presented current and in-depth knowledge of the mucosal immune system in the intestinal tract, centering on its involvement in the development and control of allergic inflammation.²⁶ We hope that our readers will enjoy the three interrelated review articles.

As original articles, several interesting clinical and basic research papers are published in this issue of AI. Questionnaires such as the asthma control questionnaire (ACQ) and asthma control test (ACT) are widely used to assess asthma control status. To adapt these questionnaires to the Japanese Asthma Prevention and Management Guideline 2015 (JGL2015), Tohda *et al.* previously developed the Japan Asthma Control Survey (JACS) questionnaire, composed of 15 questions about symptoms, activity, emotion, and treatment with regard to the optimal measurement of asthma control status in the Japanese population.²⁷ Since mild asthma patients had been dominant in the original validation study, their present study was designed to validate this questionnaire in two independent cohorts, including severe asthma patients. They demonstrate that cut-off values 8.0 and 4.8 are appropriate to differentiate well-controlled, not well-controlled, and poorly-controlled asthma as defined by the criteria in JGL2015.²⁸ The JACS questionnaire will be useful for evaluating asthma control status in clinical practice and clinical research in Japan.

Sublingual immunotherapy (SLIT) does effectively induce long-term clinical remission in allergic rhinitis, but its efficacy varies among patients. In contrast, it is known that saliva contains many immunoregulatory components including IgA, antimicrobial proteins, and microbes. Haruna *et al.* found that whole saliva from patients receiving SLIT, which probably included microbes, can induce production of substantial amounts of IL-10 in monocytes and THP-1 cells.²⁹ Saliva-induced IL-10 levels prior to SLIT were significantly higher in asymptomatic patients than in disease-onset patients following SLIT. This finding explains why the sublingual route is effective and preferable in SLIT. Saliva-induced IL-10 levels can be a predictive marker for clinical remission after SLIT.

It is difficult to diagnose asthma in children younger than five years old because no clinical method is available for objectively evaluating bronchial reactions in infants and young children. A breath sound analysis is a safe and simple method that can be applied to the clinical assessment of airway change; recent developments in this type of analysis enable us to extract more physiologically and clinically relevant information. Shioya *et al.* analyzed the breath sound of healthy infants by using a sound spectrometer and an in-house calculation software program, revealing that the middle-pitched part of the breath sound spectrum curve in the atopic infants was observed to be stronger than that of the control infants.³⁰ They hypothesized that some obstruction or dysfunction of the central airway might already exist in the infants with atopy, even in a healthy state. Breath sound analysis may be useful in assessing the airway narrowing of infants in whom asthma is developing.

FeNO reportedly reflects type 2 inflammation in the lung and serves as a useful biomarker for current eosinophilic asthma control. However, the correlation between FeNO and asthma control is sometimes inconsistent. NO is synthesized by an enzyme called NO synthase (NOS). Biopterin, a member of the pteridine group, is a cofactor assembling two inactive NOS molecules into an active form of the NOS dimer. In this issue of the journal, Kasuga *et al.* demonstrate from a prospective cohort study that the level of

serum biopterin, but not of FeNO, predicts atopic asthma control (JPAC total score) in the near future and is strongly correlated with the frequency of wheezing during exercise.³¹ These suggest that biopterin is a potential predictive biomarker for asthma control, especially in children in whom it is difficult to measure FeNO.

We offer our appreciation to all the authors for their contributions to the present issue of *Allergy International*.

Conflict of interest

The authors have no conflict of interest to declare.

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Received 29 November 2018