Secretory IgA Immune Responses as the Mucosal Frontline

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ABSTRACT

The recognition that host defenses are mediated via mucosal barriers dates back several thousand years. Ingestion of *Rhus* leaves to modify the severity of reactions to poison ivy is a centuries old practice among native North Americans. A similar practice has been carried out among Asian countries as well, where lacquer craftsmen desensitized themselves via the ingestion of sumac extracts. The modern concept of local immunity, however, developed by Besredka in the early 1900s, followed by the discovery of IgA in 1953, and its isolation and characterization in 1959. Studies in the early 1960s demonstrated the presence of IgA in a unique form in milk and, shortly thereafter, in other external secretions. These studies were followed by the discovery of the secretory component and the identification of the J chain. The remarkable immunological observations were soon complemented by the identification and characterization of the gut-associated lymphoid tissue (GALT), the findings of mucosal circulation of antigen-sensitized or reactive IgA committed B cells from GALT to other mucosal surfaces such as aero-digestive tract, genital tract and glandular tissues (e.g., salivary, lacrimal and mammary glands), and the definition of immunologically unique mucosal T cells. It should be emphasized that studies of the induction of salivary IgA responses to cariogenic bacterium, *Streptococcus mutans*, have made tremendous contribution to the characterization and understanding of the immunity at mucosal surfaces. A series of immunologically important investigations in the field of caries immunity definitively played a leadership role for the establishment of principal for the mucosal immune system. In the past decades, our concept of the mucosal immune system has been expanded to include M cells, mucosal dendritic cells and macrophages, Th1/Th2 cells, regulatory T cells and other effector cell networks, and the mucosal cytokines. Finally, the biological significance of the mucosal immune system increasingly is being realized and appreciated in the context of human infections acquired via mucosal portals of entry, including classical infectious diseases as well as newly emerging infectious diseases which lead to the desire for the development of mucosal vaccine.

Dawn of the mucosal immune system

For decades, vaccine researchers have been fighting infectious diseases without much help from one of the body's major defensive weapons, **the mucosal immune system.** Most successful vaccines to date, such as the childhood measles, mumps, and rubella immunizations, have been made from body to produce serum antibodies against disease-causing organisms. Thus, most of vaccines have been given via injection for the induction of effective systemic immunity. However, the molecular and cellular understanding of the mucosal immune system allows us to consider that the use of the system such as oral and nasal immunization leads to the induction of antigen-specific immune response in the systemic compartment in addition to the mucosal surface (see below more details). It is now plausible to propose that the current injection type vaccine can be advanced to the form of mucosal vaccine.

The part of the immune system which churns out 70% of the body's antibodies has been virtually ignored, because little was known about how it works. Membranes covered with mucous line the airways, the reproductive system, and the gastrointestinal tract, and many pathogens such as the bacterium that causes cholera and the virus that causes AIDS, first encounter the body via the mucosal epithelium. The mucosae of aero-digestive and reproductive tracts have a combined surface area of at least 400 m^2 where our body is continuously exposed to the harsh outside environments and which are of course the first ports of entry of many pathogens.

During the past 40 years, we have recognized that a distinct system of immunity (manifested by production of the IgA isotype of antibodies) exists at our mucosal surfaces (1, 2). However, as early as 1927, Besredka (3) clearly suggested the presence of the mucosal immune system as he described as a local immunity by the result obtained form the experiment with oral administration of enteric bacterial vaccines. He postulated that oral vaccination with bacteria such as shigella, salmonella, and cholera resulted in local immunity in the gut that was separate from circulating immunity.

The mucosal tissues are heavily populated with cells of the immune system: it is estimated that the intestinal lining contains more lymphoid cells and produces more antibodies than any other organ and tissue in the body (4, 5). The mucosal immune system consists of specialized local inductive sites, the organized mucosa-associated lymphoid tissue (O-MALT) and wide spread effector

sites, the diffuse mucosa-associated lymphoid tissue (D-MALT) both of which are separated from mucosal surface antigens by epithelial barriers (6). Some mucosal tissues such as vagina have no local organized MALT but rely on antigen uptake and transport into lymph nodes that drain the mucosa (7).

In either case, the first step in the induction of a mucosal immune response is the transport (or uptake) of antigens across the epithelial barrier. Following antigen processing and presentation in inductive sites, post-switched antigen-specific IgA-committed B cells proliferate locally and then migrate via the bloodstream to distant mucosal and secretory tissues. There they differentiate primarily into polymeric IgA producing plasma cells. Dimeric or polymeric IgA antibodies are transported across epithelial cells into glandular and mucosal secretions via poly Ig-receptor-mediated transcytosis. In this regard, it should be emphasized that studies of the induction of salivary antibodies to antigenic components of the cariogenic bacterium, *Streptococcus mutans*, part of the efforts for the development of carries vaccine have contributed to a fuller understanding of immunity at mucosal surfaces (8).

Discovery of Mucosal IgA (Secretory IgA:S-IgA, a launch for the mucosal immunity)

The discovery by Tomasi and coworkers (9) that IgA is the major immunoglobulin found in human external secretions, and subsequent work by others that most mammalian species possess IgA as the predominant immunoglobulin in secretions, have provided the impetus for studies of the mucosal immune system in health and disease. The observation that mucosal tissues contain many localized IgA producing plasma cells, coupled with findings that local antigen exposure results in the presence of S-IgA antibodies at that site, led many investigators to assume that S-IgA responses were entirely operated by the local immune system in nature. The elegant studies of Ogra and coworkers (10) showed that immunization of the lower alimentary tract with polio vaccine resulted in the induction of S-IgA antibodies in this area. This work was one of the first to provide convincing evidence that local administration of living antigen to mucosal sites resulted in the induction of antigen-specific IgA antibody response in the same surface area.

Peyer's patches are primary inductive sites for IgA responses and existence of a common mucosal immune system

The classical studies of Craig and Cebra (11) suggested that Peyer's patches (PPs) contain IgA precursor B cells that can populate the lamina propria of the gastrointestinal tract and become IgA producing plasma cells. These studies were the first to suggest a mucosal migratory pathway involved in the IgA response. Subsequent studies have shown that oral administration of antigens leads to the production of S-IgA antibodies in the gut as well as in secretions at distant mucosal sites such as salivary and mammary glands (11). In addition, it is well known that human colostrums and milk contain antibodies to gastrointestinal bacteria, including *Escherichia coli* (12), and to the oral bacterium *Streptococcus mutans* (13). Furthermore, studies done by Robertson and Cebra (14) provided strong evidence that following antigen exposure of intestinal tissue with a Peyer's patch (PP), IgA precursor B cells migrate from the patch via lymphatics to the bloodstream and thereby reach the lamina propria of other regions of the gastrointestinal tract, where they become mature IgA synthesizing plasma cells. These elegant studies made significant contribution for the concept of the common mucosal immune system which is consisted of the inductive (e.g., PP) and effector (e.g., lamina propria region) sites.

Molecular basis of PP development

PPs occur mainly in the ileum and less frequently in the jejunum in humans. By definition, they consist of at least five aggregated lymphoid follicles but can contain up to 200 such organized structures (15). Human PP anlagen composed of $CD4^+$ dendritic cells (DCs) can be seen at 11 weeks of gestation, and discrete T- and B- cell areas occur at 19 weeks, but no germinal centers appear until shortly after birth, reflecting dependency on stimulation from the environment, a process that also induces follicular hyperplasia (16). Macroscopically visible PPs in humans increase from approximately 50 at the beginning of the last trimester to 100 at birth and 250 in the middle teens, then diminish to become approximately 100 between 70 and 95 years of age (15).

The initial steps involved in murine PP development have been studied in some detail in mice. A cluster of vascular cell adhesion molecule 1^+ (VCAM1)/intracellular adhesion molecule 1^+ (ICAM1) cells develops in the upper small intestine beginning at embryonic days 15 to 16, followed by the presence of cells expressing the IL-7 receptor (IL-7Rα) at day 17.5 (17), which appear to be the anlagen of the patch. Mice defective in IL-7Rα gene expression fail to form mature GALT (17). It now appears that IL-7-IL-7Rα triggering results in up-regulation of lymphotoxin (LT)α1β2 membrane expression by lymphoid cells, including those in developing PPs (18-21). Furthermore, mice that lack LTα or LTβ or that have been treated *in utero* with a fusion protein of LTβ receptor-immunoglobulin fail to develop PPs or systemic lymph nodes (22). In addition, alymphoplasia (aly/aly) mice with a mutation in the NFκB-inducing kinase (23), which appears to act downstream of LTα1β2-LTβ receptor signaling, also fail to develop PPs. These findings together, the initiation of tissue genesis of PP depends on the group of the mucosal organogenesis cytokine family of IL-7/IL-7R and LTα1β2-LTβR.

Unique characteristics of PP : M cells

Murine PPs contain a dome, underlying follicles (B-cell zone with germinal centers), and parafollicular regions enriched with T cells. The specialized epithelial cells covering PPs were called an FAE (follicle-associated epithelium) cell because it characterized the uniqueness of the organized lymphoid tissues in the gastrointestinal tract including the presence of antigen-sampling M cells (24). M cells were later named for its unique topical structure of microfold/membraneous with the pocket formation at the basement membrane and the entire epithelium covering mucosa-associated lymphoreticular tissue (MALT)

such as PPs is now commonly described as an FAE type (25, 26). M cells have short microvilli, small cytoplasmic vesicles and few lysosomes. Microorganisms and complex antigens can be engulfed by M cells, and the uptake and transcellular passage of luminal antigens, including proteins and small particles through the cells, has been reported (27-29). Although the biological importance of M cells is highly appreciated, the origin of the cells is still unknown. In several years ago, a method for generating M cells *in vitro* has been reported (30, 31). Co-culture of an intestinal epithelial cell (IEC) line Caco-2 with mouse PP T and B cells or with a human B cell line (Raji) transformed polarized and differentiated IEC into M cells. This observation indicates that M cells are derived from an epithelial cell-lineage under the influence of lymphocytes, especially B cells, possess signaling molecules for the induction of M cells, but the mechanisms behind M cell development still remain to be elucidated.

PPs have all the immunological elements for mucosal S-IgA response

PPs also contain all the immune-competent cells needed for the induction of antigen-specific IgA immune response, including those of antigen presenting cells (APC including dendritic cells, macrophages and intestinal epithelial cells), IgA committed B cells and Th1 and Th2 lymphocytes. After the uptake of antigens through M cells, the antigens are processed and presented by professional APCs. A major APC population in the subepithelial region of PPs is characterized as dendritic cells (DCs) (32). PP contains at least three distinct subsets of mucosal DCs characterized by the expression patterns of surface molecules including CD11b and CD8α (33, 34). The kinds of immune responses evoked by each subset also are variable, and distinct: the generation of Th2 cells for the induction of an IgA response, the induction of Th3/Tr1 cells and/or inducible CD25 Tr cells for oral tolerance and the generation of Th1 cells for humoral and cell mediated immune responses.

Mucosal dendritic cells for IgA response

It should be postulated that major population of DCs isolated from a variety of mucosal sites (PP, lamina propria, mesenteric lymph nodes and lung) have a tendency to induce T helper type 2 (Th2) responses in *in vitro* T cell priming assays and to express regulatory/suppressive cytokines such as IL-10 and possibly transforming growth factor-β (33, 35, 36). Moreover, Hachimura et al. reported that mucosal DCs and in particular the $CD11c^+CD11b^+CD8\alpha$-DC subset isolated from Peyer's patches, which preferentially polarizes antigen-specific T cells to produce Th2 cytokines and IL-10 in vitro, promote IgA production by naïve B cells, which is mediated by IL-6 and T cell help (37). These findings indicate that the inductive site contains all the necessary DC subsets for the simultaneous induction and regulation of active (e.g., S-IgA) as well as quiescent (e.g., oral tolerance) immune responses.

Mucosal T cells for IgA response

Our earlier study clearly suggested that PPs possess antigen-specific helper T cells, which support proliferation and differentiation of surface IgA positive ($sIgA^+$) B cells into IgA producing plasma cells (38). Although the study preceded discovery of Th1 and Th2 subsets, these clones would, in retrospect, have properties of Th2-type cells. Today it is obvious that $CD4^+$ Th cells and derived cytokines from mucosal inductive sites can support the IgA response (39). For example, depletion of $CD4^+$ T cell subsets *in vivo* with monoclonal antibodies or by knockout of the CD4 co-receptor gene markedly affects on the induction of mucosal IgA responses (40, 41). In addition, PP $CD4^+$ T cell subset producing TGF-β is a key element for the gene conversion of isotype switching for $sIgM^+$ B cells to $sIgA^+$ B cells in the germinal centers of distinct follicles beneath the dome area of PP (42, 43).

For the B cell terminal differentiation of $sIgA^+$ B cells to IgA plasma cells for the generation of S-IgA, IL-5 and especially IL-6, possibly in combination with other cytokines produced by Th2 cells in the mucosal effector sites, appear essential for the continued generation of IgA producing plasma cells (44).

It would be too simplistic to conclude that Th2 type cells and their derived cytokines such as IL-5 and IL-6 are the only cytokines important in the generation of S-IgA responses (45). IL-2 also synergistically augmented IgA synthesis in B cell cultures in the presence of lipopolysaccharide (LPS) and TGF-β (43). Although IFN-γ is not directly involved in the enhancement of IgA B cell responses, this cytokine has been shown to enhance the expression of poly Ig receptor (or secretory component: SC), an essential molecule for the formation and transport of S-IgA (46). B cells activated through surface immunoglobulin in the presence of IFN-γ became potent APCs for T cells (47). In summary, an optimal relationship for the cross communication between Th1 and Th2 derived cytokines is essential for the induction, regulation, and maintenance of appropriate IgA responses in mucosa-associated tissues.

PP independent IgA responses

Progress of molecular basis of PP organogenesis revealed that the progeny of mice treated with the fusion protein of LTβ receptor and Ig lack PPs but not mesenteric lymph nodes (MLNs). Thus, it allows the investigator to address the question of whether PPs are essential or not for the induction of antigen-specific IgA response in vivo. Yamamoto et al. took advantage of this unique in vivo model (22) and examined the importance of PPs for the induction of mucosal IgA antibody responses. Oral immunization of PP null mice with chicken ovalbumin (OVA) plus cholera toxin as mucosal adjuvant resulted in antigen specific mucosal IgA (and serum IgG) responses. OVA-specific $CD4^+$ T cells of the Th2 type were induced in MLN (and spleen) of PP null mice. In contrast, when TNF and LT-α double knockout mice, which lack both PPs and MLN, were orally immunized with OVA plus cholera toxin, neither mucosal IgA (nor serum IgG) anti-OVA antibodies were induced. These results clearly show that the MLN plays a crucial role than had been appreciated for the induction of mucosal IgA responses after oral immunization, suggesting that PPs are not indispensable for the induction of mucosal IgA responses in the gastrointestinal tract. In addition, the result leads

to the idea for the presence of additional antigen sampling and/inductive sites for PP-independent Ig A responses.

Mucosal IgA responses to commensal bacteria are PP independent

MacPherson et al. reported that the induction of commensal-specific IgA is independent of T helper cell activity and of the organization of lymphoid tissues such as PPs, reflecting an evolutionarily primitive form of specific immune defense (48). A related, intriguing observation is that up to 40% of IgA producing cells in murine intestinal lamina propria arise from a pool of B-1 precursors derived from the peritoneal cavity (49). They give rise to polyreactive natural S-IgA antibodies, particularly directed against polysaccharide antigens from commensal bacteria. In addition, Fagarasan et al. proposed an alternative pathway in which sIgM$^+$ B cells in the lamina propria (LP) switch to production of the IgA isotype without the need for T cell help (50). In this study, the authors speculate that dendritic cells sample antigen from the lumen and present it to B1 cells, which under the influence of cytokines derived from LP stromal cells trigger the process of isotype switching and differentiation to IgA producing plasma cells. In most recent work by MacPherson and Uhr, they characterize the active transport of live commensals by mucosal DCs from the mouse gut lumen to the intestinal mesenteric lymph nodes. The DCs carrying their commensal load do not stray beyond these lymphoid tissues, preventing a systemic infection and ensuring a commensal specific IgA response that is restricted to the gut mucosa. In this regard, Reinecker et al. (51) reported that intestinal lamina propria CD11b$^+$ DCs expressing CX3CR1 chemokine receptor were found to form transepithelial dendrites, which enable the cells to directly sample luminal antigens. Thus, CX3CR1-dependent processes, which control host interactions of specialized DCs with commensal and pathogenic bacteria, may regulate immunological tolerance, mucosal inflammation as well as humoral immune responses such as mucosal IgA antibody production.

Gut-homing lymphocyte imprinting by mucosal dendritic cells

Effector memory lymphocytes that arise in response to antigens in the alimentary tract express mostly intestinal homing receptors, particularly the integrin $\alpha4\beta7$ and CCR9, the receptor for TECK/CCL25, a chemokine expressed in the small intestine (39). In vivo studies have shown that the microenvironment in which lymphocytes encounter antigen somehow instructs them about their homing preference (52). In addition, in vitro activation of naïve T cells with DCs from PPs or MLNs, but not from peripheral lymph nodes (PLNs) or spleen, induces (instructs) effector lymphocytes with high expression of $\alpha4\beta7$ and CCR9 and the capacity to migrate to the small intestine (53, 54). The mechanism responsible for this imprinting of gut specificity was recently and elegantly shown by Iwata et al (55). They showed that T cell exposure to the vitamin A metabolite retinoic acid induced gut homing receptors and the ability to migrate to the small intestine. Importantly, many DC from PP and MLN but few from PLN or spleen expressed the prerequisite enzymes for oxidative conversion of vitamin A to retinoic acid, and inhibitors of these enzymes rendered intestinal DC incapable of inducing $\alpha4\beta7^+$T cells.

S-IgA responses in oral cavity

The oral cavity is part of the mucosal linings of the body and shows structural similarities with mucosal tissues in the gut and lungs, among other organs (56). It is also considered as the initial entry for the aero-digestive tract where all of the foreign and environmental antigens are taken up. Oral health depends on the integrity of the oral mucosa and its mucin coating, which together normally prevent the penetration of microorganisms and macromolecules that might be antigenic and/or pathogenic. The mucosa is normally protected by both immunological arms of innate and acquired defense mechanisms. Innate elements include mucins, lysozyme, lactoferin, lactoperoxidase, and various antimicrobial peptides such as histatins, β-defensins, and protease inhibitors, while the acquired mechanisms include immune cells of Th1/Th2, CTL and IgA committed B cells as well as S-IgA and other Ig isotypes. Oral epithelial cells themselves are reactive and express Toll-like receptors and produce a variety of regulatory and inflammatory cytokines upon activation (56). However, it should be noted that the usage and expression of TLR family seems to be quite unique at the mucosa where continuously exposed to abundant numbers of environmental antigens and stimuli, when compared with the systemic compartment since the latter is situated more sterile condition (57)

Although the oral cavity displays similarities with other parts of the mucosal immune system, some of its immune mechanisms differ from those found elsewhere. Oral immune system includes those that are part of the S-IgA immune system, emanating from major and minor salivary glands, and those from the systemic IgG immune system, emanating from crevicular fluid or within the gingival and mucosal tissues. Thus, oral cavity is protected by the immunological benefit of both mucosal and systemic immune systems.

The most striking difference between the oral cavity and the tissue lining the remainder of the gastrointestinal tract is the presence of the hard tissue, teeth. The junction between the teeth and mucosa allows a greater access of serum proteins (56) and immune cells to the mucosal surface than is found in other mucosae and thus presents an interface between the systemic and mucosal immune systems, either of which may influence the control and /or development of diseases in the anatomical vicinity. There is also exposure of a unique epithelium, the junctional epithelium around the necks of the teeth, to microbial challenge, and this epithelium is compromised in periodontal diseases (56).

The main sources of S-IgA into the oral cavity are major salivary glands such as parotid and submandibular glands. It has been shown that oral and/or nasal immunization is effective in the induction of antigen-specific IgA antibody producing cells in these salivary glands which account for the generation of S-IgA antibodies in saliva (8, 58). The total volume of saliva produced per day is probably between 750 and 1000 ml.

Most of the IgA in saliva is dimeric, but 5 to 10% is monomeric. In case of human, the IgA1 to IgA2 subclass ratio is about 55:45, in which the subclass ratio is similar to that seen in the intestinal LP. In whole saliva, the concentration of S-IgA is approximately 200 mg/1000 ml. Thus, S-IgA antibodies produced by the oral immune system via the use of concept of CMIS are not only a major element of mucosal immunity for the oral cavity but also contribute as a major source of the secretory form of antibodies for the rest of digestive tract as well.

Immunology of dental caries

Dental caries is one of the most common diseases of humankind. In spite of recent reductions in the rate of decay in western societies, the prevalence of caries in developed countries remains at greater than 95% of the population (56). Caries is still increasing in the developing countries with the increased consumption of refined sugars.

Dental caries is defined as the localized destruction of hard tissue by bacterial action. It requires both specific cariogenic bacteria, which are capable of producing acid, and carbohydrate in the diet, which can be metabolized by these bacteria and helps their colonization of the tooth surface (59). Dissolution of the hydroxyapatite crystals seems to precede the loss of organic components of both enamel and dentine, and thus demineralization is thought to be caused by acids resulting from the bacterial fermentation of dietary carbohydrates (59). Not all surfaces of the tooth are equally afflicted, and areas protected from cleansing such as the fissures and areas between the teeth are much more susceptible to decay.

The concept of immunity to caries depends on the demonstration that caries is a bacterial infection. Although vaccination against dental caries was attempted in the 1930s (8, 59), the real impetus for development of vaccination came with the demonstration that caries could not occur in the absence of bacteria whatever the diet, and later, that specific bacteria were needed (59).

As much as the anatomical location of tooth is an immunologically unique environment where it receives benefit of both the systemic as well as mucosal immune systems, both routes of immunizations have been examined for the generation of antigen-specific immune responses to mutans streptococci in humans, and for the protective effects in vaccination experiments in animal models (8, 59). Two different possibilities have been proposed for the mechanisms of immunological control against dental caries (59). One hypothesis, put forward primarily by British groups, is that serum IgG antibodies are mainly responsible for the protective effect, whereas American workers suggest that S-IgA in saliva inhibits adherence of *S. mutans* to tooth surfaces by using rodent caries models. However, it should be noted that these two mechanisms are not mutually exclusive. And the expansion of our knowledge in the uniqueness of oral immunity, the use of both immunological arms is most effective for the control of dental caries.

For example, Smith et al. (60) demonstrated that local immunization with formalinized whole cells of *S. mutans* resulted in an enhanced salivary IgA response and reduced caries development in both conventional and gnotobiotic rats. Furthermore, Michalek et al. (61) reported that the ingestion of formalin-treated cells of serotype g mutans streptococci has been shown to stimulate specific S-IgA antibody response in saliva and milk but not in serum of rats. Orally immunized rats developed significantly fewer carious lesions than nontreated control rats. Moreover, our studies demonstrated that nasal immunization of mice with a surface protein antigen of *S. mutans* with non-toxic mucosal adjuvant elicited salivary IgA antibody that inhibits colonization of *S. mutans* in murine oral cavity (58, 62).

Antigen-specific salivary IgA antibodies in humans can be induced by ingestion of capsules filled with *S. mutans* organisms (63), and recently nasal immunization with glucosyltransferase in humans has been shown to elicit both salivary IgA and serum IgG antibodies (64). No extended studies have been performed to see the inhibitory effect of such antibody on caries development in humans. However, artificially created *S. mutans*-specifc S-IgA antibodies by the use of transgenic plant system clearly showed that the application of the antibody influenced on the incidence of caries development (56). Although the issue for the execution of caries vaccine for the public health remains to be matter of debate, the concept of caries vaccine definitively triggered a series of outcome for the understanding of the mucosal immune system. It provided a fact that the immunological basic research initiated in the field of Dentistry contributed for the discovery and understanding of one of major arms of the host immune system, namely the mucosal immune system which is now well accepted in the scientific field of Immunology, and used for possible application of other infectious and immunological diseases threatening mankind.

SUMMARY

In this review, we described IgA comprises the body's major isotype of antibody and the bulk of the body's IgA producing cells reside in the various mucosal and exocrine sites. The production of IgA at mucosal surfaces is strictly regulated by the integrated cross communication consisting of mucosal IgA^+B cells, mucosal T cells, mucosal dendritic cells, and epithelial cells. Although it has long been recognized that a major source of IgA plasma cells at mucosal surfaces is the organized lymphoid tissue such as Peyer's patches, it was recently revealed that PP null mice can also sustain mucosal IgA responses. Mucosal dendritic cells may be specialized in inducing a non-inflammatory environment and in providing help B cells to promote IgA producing plasma cells via the activation of Th2 cells. In this regards, the induction of commensal bacteria specific IgA^+B cells is independent of T helper activity, but possibly dependent on mucosal dendritic cells expressing CX3CR1 chemokine receptor. In this context, the mesenteric lymph nodes act as inductive site for the generation of secretory IgA antibodies that prevent the microflora from reaching the systemic compartment of the host immune system and from eliciting a damaging inflammatory response.

Although it is likely that the secretory IgA responses play a crucial role for the caries immunity, the induction

and regulation of the S-IgA responses in oral cavity still remains puzzling. Mucosal dendritic cells in oral cavity such as Langerhans dendritic cells could be indispensable for the induction and regulation of Th2 cells and IgA^+B cells which mediate the humoral immune responses to cariogenic as well as periodontal pathogens. However, it still remains vague where and how the Langerhans-type dendritic cells drive T cells as well as B cells to expand and differentiate for the development of Th2-mediated IgA responses. Future studies will address more detailed molecular and cellular basis for the immune responses occurred in oral cavity.

Dedication to the late Dr. John Cebra

The year 2005 was very exciting but also very sad year for among mucosal immunologists. We had experienced scientific and social excitements of the12th International Congress of Mucosal Immunology in Boston, June in 2005. At that time John's numerous scientific contribution for the area was recognized by the first Society of Mucosal Immunology (SMI) Distinguished Science Award. During the award ceremony, we all respected his accomplishment and were glad to see his smile. Unfortunately, we recently leaned sad news from Pennsylvania that he has passed away from his long fight for the illness which he never expressed in the public. He was one of the founders and frontiers of Mucosal Immunology which we all now enjoy the scientific excitement of this fascinating field. His smile during the award ceremony still floats before our eyes. Thanks John for your scientific contribution for the establishment of Mucosal Immunology.

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