

Keynote Address

Mucosal Immunology: The Gateway to the Immune System

Overview of the Innate and Adaptive Mucosal Immune System: Linking Immune Development in the Gut to Other Mucosal Sites and the Periphery

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The power of our immune system is a result of co-evolution in which commensal bacteria and parasites have shaped the mechanisms of both innate and adaptive immunity.¹ Notably, the adaptive immune system developed rather late in the phylogeny, and most species survive without it. Mammals, however, possess extremely sophisticated adaptive defense mechanisms of both systemic and mucosal type. A great redundancy exists in both immune systems, providing robustness to preserve homeostasis.

Innate and Adaptive Immunity

The attempt of a microbe to invade the body is immediately counteracted by the innate immune defense, which comprises surface barriers (epithelial linings, mucus, ciliary function, and peristalsis), soluble factors (pH of body fluids, antimicrobial peptides, and proteins), phagocytes (granulocytes and macrophages), and dendritic cells (DCs), which are specialized for presenting antigens to T cells. These mechanisms restrict invasion of the body by foreign components and inhibit their persistence within the tissue. Such challenge of the innate system often leads to inflammation but at the same time to activation of the adaptive system, which by its effector T cells, regulatory T (Treg) cells, and B cells aids the recovery from a noxious impact.

In contrast to the antigen-specific surface receptors of T and B cells, which show a random and highly diverse repertoire, the recognition molecules for innate immunity are encoded in the

germline.² This system is therefore quite similar among healthy individuals but receptor mutations may give rise to disease-promoting polymorphism. Innate responses show no classical memory—that is, re-exposure to a pathogen normally elicits the same type of potentially proinflammatory reaction, although downregulation in the face of subsequent infection has been observed, probably to preserve tissue integrity.³

The innate receptors sense conserved structures that are essential for microbial survival and present in a broad range of microbes, including endotoxin (or lipopolysaccharide [LPS]), teichoic acids, and unmethylated CpG motifs of DNA.² Such structures generally are referred to as pathogen-associated molecular patterns (PAMPs), but they also occur in commensal bacteria and should preferably be referred to as microbe-associated molecular patterns (MAMPs). The intestinal microbiota induces distinct programming of the innate immune system, which could partly explain tolerance by the host.⁴ Such a tolerogenic response is especially apparent for mucosal epithelia.⁵

The cellular receptors that recognize PAMPs/MAMPs are called pattern recognition receptors (PRRs), many of them belonging to the so-called Toll-like receptors (TLRs). PRRs are expressed by macrophages and DCs, as well as by a variety of other cell types such as T cells, B cells, and epithelial cells. The engagement of PRRs may cause cellular activation (mainly via the transcription factor nuclear factor-kappa B [NF- κ B]), which in the case of antigen-presenting cells (APCs) such as DCs leads to maturation accompanied by production of cytokines and upregulation or downregulation of cell-surface molecules according to strictly defined kinetics.⁶

Engagement of other types of receptors on phagocytes, including immunoglobulin (Ig) Fc receptors and complement receptors, triggers phagocytosis and elimination of invading microorganisms. Although pathogens have evolved mechanisms to evade the innate defense (eg,

bacterial capsules), they will usually be eliminated when an adaptive response reinforces innate immunity by providing specific antibodies directed against the invading pathogen or its toxins. Thus, innate immunity influences the character of the adaptive response, and the effector arms of adaptive immunity support several innate defense mechanisms. The nonspecific biological amplification collectively triggered by them is referred to as immune reaction, or hypersensitivity/allergy if clinical harm is observed as inflammatory disease.

Strategies of the Mucosal Immune System

The mucosal immune system provides a first defense line that reduces the need for elimination of invading exogenous antigens by proinflammatory systemic immunity. To maintain homeostasis, the mucosal immune system has, through evolution, developed two layers of adaptive noninflammatory defense: (a) immune exclusion provided primarily by secretory antibodies to limit epithelial contact and penetration with host invasion of microorganisms and other potentially dangerous antigens, and (b) immunosuppressive mechanisms to inhibit overreaction against innocuous luminal antigens (Fig 1).

[insert Fig 1]

The latter strategy, which is referred to as “oral tolerance” when induced via the gut,^{4,7} depends largely on the development of Treg cells in mesenteric lymph nodes to which mucosal DCs carry dietary and microbial antigens and become conditioned for induction of Treg cells. Mucosally induced tolerance probably involves additional suppressive mechanisms, which together with Treg cells, contribute to the fact that overt and persistent hypersensitivity to food is

relatively rare. A similar downregulatory tone of the immune system normally exists against commensal bacteria.^{5,8}

Mucosal tolerance appears rather robust in view of the fact that more than a ton of food may pass through the gut of an adult every year. After a meal, intact dietary antigens are taken up in the nanogram range, usually without causing harm. However, the neonatal period is critical, both with regard to infections and to priming for allergic disease, because the epithelial barrier and the immunoregulatory network are poorly developed.^{9,10}

Experiments have demonstrated a crucial role of microbial colonization in establishing¹¹ and regulating¹² the epithelial barrier. At least in mice, the beneficial effects of commensal bacteria on the barrier function are largely mediated via PRRs expressed by the gut epithelium, particularly TLRs.^{13,14} Polarized epithelial cells have the ability to dampen the proinflammatory effect of PRR-mediated signals coming from the luminal side.⁵ However, after bacterial invasion, PRR signaling from the basolateral side results in a high level of NF- κ B activation, with enhanced release of defensins to combat the infection.⁵

Secretory Immunity Reinforces the Epithelial Barrier

The mucosal and systemic immune systems differ in many structural, cellular, molecular, and functional ways.¹⁵ Mucosal immunity is most abundantly expressed in the gut, and the intestinal mucosa of an adult contains at least 80% of the body's activated B cells—terminally differentiated to plasmablasts and plasma cells (PCs).¹⁶ Thus, the gut is by far the largest antibody-producing organ in the body.

Most mucosal PCs produce dimeric IgA, which along with pentameric IgM that likewise contains a polypeptide called “joining” (J) chain, can be actively exported by secretory

epithelia.¹⁶ This external transport is mediated by the polymeric Ig receptor (pIgR), also known as membrane secretory component, or SC.¹⁷ Immune exclusion is performed mainly by secretory (S)IgA, and to a lesser extent SIgM, in cooperation with innate nonspecific defenses (Table and Fig 2). In newborns and people with selective IgA deficiency, SIgM antibodies are of greater importance than in healthy adults.¹⁸

[insert Table, Fig 2]

Immune-inductive mucosa-associated lymphoid tissue (MALT) resembles lymph nodes with B-cell follicles, intervening T-cell zones, and a variety of APCs such as macrophages and DCs (Fig 3), but there are no afferent lymphatics.¹⁵

[insert Fig 3]

Exogenous stimuli therefore come directly from the mucosal surfaces via a follicle-associated epithelium containing specialized M cells, probably aided by DCs, which may penetrate the epithelium with their processes.⁵ In the intestine, induction and regulation of mucosal immunity hence takes place primarily in Peyer's patches, together with other parts of gut-associated lymphoid tissue (GALT) and the gut-draining mesenteric lymph nodes, but also to some extent at the effector sites to which activated T and B cells home (Fig 3).

Retinoic acid, derived from vitamin A in the diet, exerts a positive impact on both differentiation and gut homing of the precursors for IgA-producing PCs.¹⁹ Moreover, the propensity of the mucosal immune system to generate cross-reactive antibodies is probably explained by the extensive innate drive imposed on it by the abundant commensal microbiota via PPRs. Thus, experiments have documented a role of Toll-like receptors for B-cell differentiation in MALT structures.²⁰

Although immunological memory is generated after mucosal priming, this may be masked by a self-limiting SIgA response shielding the inductive lymphoid structures, particularly the Peyer's patches of GALT.²⁰ An additional complication is the regionalization of the mucosal immune system with regard to migration of mucosal memory/effector B cells to various effector sites. Nasal vaccines that target nasopharynx-associated lymphoid tissue (NALT) of Waldeyer's ring and cervical lymph nodes elicit both regional mucosal and systemic immunity but do not regularly furnish the small intestine with activated B cells.^{16,21} Such disparity of mucosal B-cell homing is masked in the intestinal lumen of rodents where much of the SIgA in the upper part of the gut is derived from bile.²²

Ethical constraints restrict direct tracking of immune-cell migration throughout the human body in vivo. We therefore used deletion of the IgM heavy-chain constant-gene (C μ) segment as a marker to provide a dispersal signature of an effector B-cell subset (IgD⁺IgM⁻CD38⁺) induced selectively in human tonsils.²¹ By DNA analysis, the C μ deletion identified dissemination of such blasts and their PC progeny to peripheral blood, lymph nodes, and bone marrow, as well as to mucosae and glands of the upper airways. Also the endocervix was often positive while the small intestine was mainly negative, as could be expected from the identified homing-molecule profile of the marker cells—with relatively low levels of integrin α 4 β 7 and the CC chemokine receptor 9 (α 4 β 7^{int./low}CCR7^{high}CCR9^{low}CCR10⁺CD62L^{high}). Of further importance, the circulating cells abundantly expressed CD62L (L-selectin) and CCR7, which provided a mechanism for integration of respiratory and systemic immunity. Importantly, lactating mammary glands received precursors for IgA⁺ PCs, both from GALT and NALT.⁹

The Vulnerable Neonatal Period

IgA-producing PCs generally are undetectable in the mucosae before 10 days of age, but thereafter they increase rapidly. However, IgM-producing PCs often remain predominant up to 1 month of age.¹⁸ Usually, intestinal IgA increases little after 1 year of age. A much faster establishment of secretory immunity often is seen in developing countries with a heavy microbial load. The mucosal PC development reflects the progressive microbial stimulation of MALT.¹⁶ Accordingly, only occasional traces of SIgA and SIgM occur in intestinal juice during the first postnatal period, whereas some immunoglobulin G (IgG) often is present, reflecting paracellular “leakage” from the lamina propria, which after 34 weeks of gestation contains readily detectable maternal IgG.¹⁸ In addition, some IgG may be actively exported by epithelial neonatal FC receptor (FcRn).²³ More importantly, both retinoic acid from vitamin A and butyrate derived from microbial fermentation of oligosaccharides in food (and breast milk) can upregulate the epithelial pIgR/SC expression and thereby enhance the SIgA export.²⁰

Uptake of SIgA antibodies from breast milk via the neonatal gut mucosa is negligible, however, and of no immunological importance in humans, except perhaps in preterm infants.²⁴ So-called gut closure normally occurs before birth, but the mucosal barrier may be inadequate up to 2 years of age. Although the mechanisms involved remain poorly defined, SIgA from breast milk and development of the infant’s immune system are two related variables in this process.

Animal experiments have suggested that SIgA-containing immune complexes may be taken up via M cells of GALT and guide the induction of the breastfed infant’s immune system to a homeostatic response.²⁵ Altogether, therefore, it is not surprising that recent meta-analyses show that breastfeeding protects against allergic disease and several other immune-mediated disorders, driven by exogenous factors in developed societies.²⁶ The same is true for celiac disease.²⁷ Notably in this context, pIgR knockout mice that lack secretory antibodies show reduced

epithelial barrier function and increased uptake of antigens from food and commensal bacteria.²⁸
²⁹ They therefore have a hyperreactive immune system and show predisposition for systemic anaphylaxis after sensitization; however, this development is counteracted by enhanced oral tolerance induction as a homeostatic backup mechanism.³⁰

Conclusions

Many variables influence mucosally induced tolerance and productive IgA-dependent secretory immunity. Some of these variables are reciprocally modulated to achieve homeostasis. Increased epithelial permeability is an important primary or secondary event in the pathogenesis of many diseases, including allergy, celiac disease, and inflammatory bowel disease. The barrier function is determined by the individual's age (eg, preterm vs term infant); genetics; mucus; interactions between mast cells, nerves, and neuropeptides; concurrent infection; and the mucosa-shielding effect of SIgA provided by breast milk or produced by the infant's gut. The remarkable output of SIgA during feeding serves as an optimally targeted passive immunization of the breastfed infant's gut as well as a positive homeostatic feedback loop.

Many studies indicate that allergy is associated with delayed or impaired development of the IgA system. This is not surprising because secretory immunity is of great importance for the intestinal barrier function. SIgA not only maintains mutualism with the indigenous microbiota but also forms the first line of defense against commensals and pathogens, as well as other harmful agents. In addition, epithelial integrity depends on interaction with microbial factors (MAMPs) from the environment and particularly from the indigenous microbiota, both by direct engagement of epithelial PRRs and induction of mucosal tolerance via different immunosuppressive mechanisms, including tolerogenic APCs and Treg cells.

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Table. Antimicrobial Effects of SIgA Antibodies

- SIgA is dimeric/polymeric, therefore, exerting efficient microbial agglutination and virus neutralization
 - SIgA performs noninflammatory extracellular and intracellular immune exclusion by inhibiting epithelial adherence and invasion
 - SIgA exhibits cross-reactive (“innate-like”) activity and provides cross-protection in the herd
 - SIgA (particularly SIgA2) is quite stable (bound SC stabilizes both isotypes of IgA)
 - SIgA is endowed with mucophilic and lectin-binding properties (via bound SC in both isotypes and mannose in IgA2)
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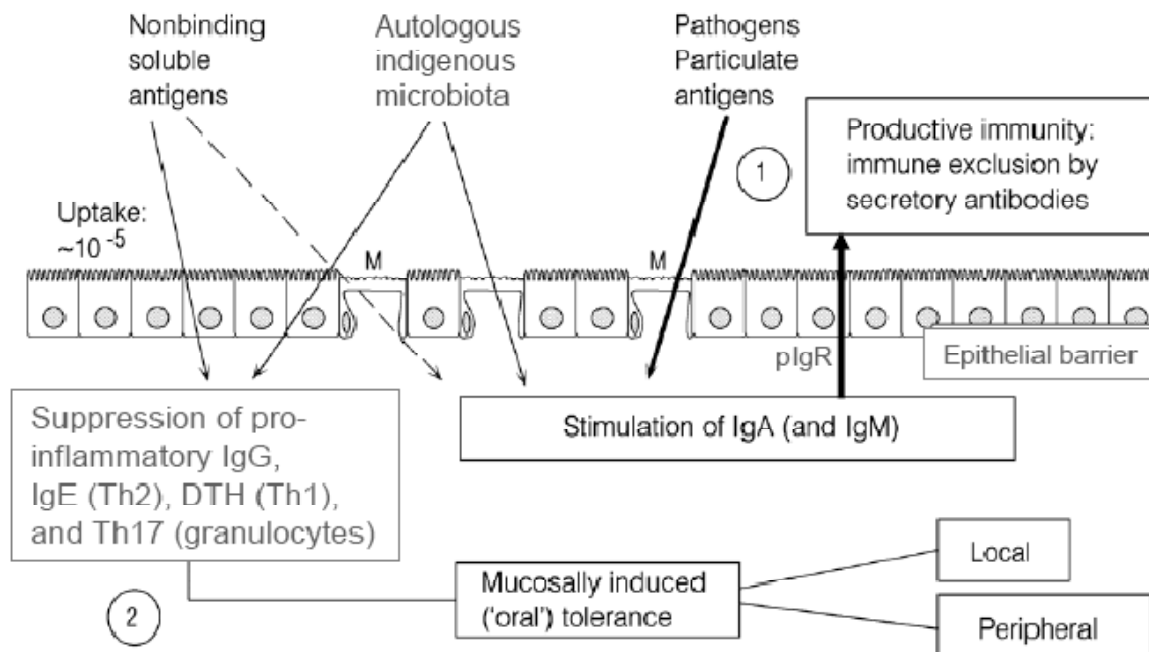


Fig 1. Schematic depiction of two major noninflammatory immune mechanisms operating at mucosal surfaces.

(1) Productive immunity providing immune exclusion limits epithelial colonization of pathogens and inhibits penetration of harmful foreign material. This first line of defense is principally mediated by secretory antibodies of the IgA (and IgM) class in cooperation with various nonspecific innate protective factors (not shown). The secretory antibodies are actively exported by the epithelial polymeric Ig receptor (pIgR), also called membrane secretory component. Secretory immunity is preferentially stimulated by pathogens and other particulate antigens taken up through thin M cells (M) located in the dome epithelium covering inductive mucosa-associated lymphoid tissue. (2) Innocuous soluble antigens (eg, food proteins; magnitude of uptake indicated) and the indigenous microbiota are also stimulatory for secretory immunity (graded arrows), but induce mainly suppression of proinflammatory humoral immune responses (IgG and Th2 cytokine-dependent IgE antibodies), as well as Th1 cytokine-dependent delayed-type hypersensitivity (DTH) and Th17-dependent granulocytic reactions. This homeostatic Th-cell balance is regulated by a complex phenomenon called “oral tolerance” when induced via the gut, in which induction of regulatory T cells is important. Their suppressive effects can be observed both locally and in the periphery.

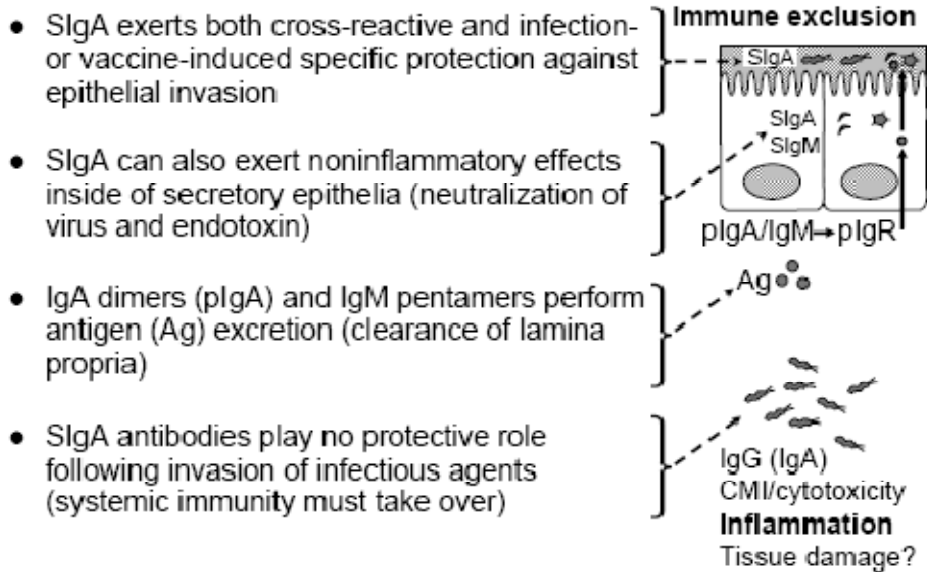


Fig 2. Different principles of SIgA-mediated contribution to mucosal homeostasis. In addition to immune exclusion at the epithelial surface, the pIgR-mediated external transport of dimeric IgA and pentameric IgM (pIgA/IgM) might be exploited for intraepithelial virus or toxin neutralization and excretion of exogenous antigens back to the lumen. However, when infection with persistent pathogen invasion occurs, systemic immunity must take over to eliminate noxious antigens and thereby save life. This involves potent proinflammatory mechanisms such as complement activation by IgG antibodies, cell-mediated immunity (CMI), and cytotoxicity, which all may cause tissue damage.²⁰

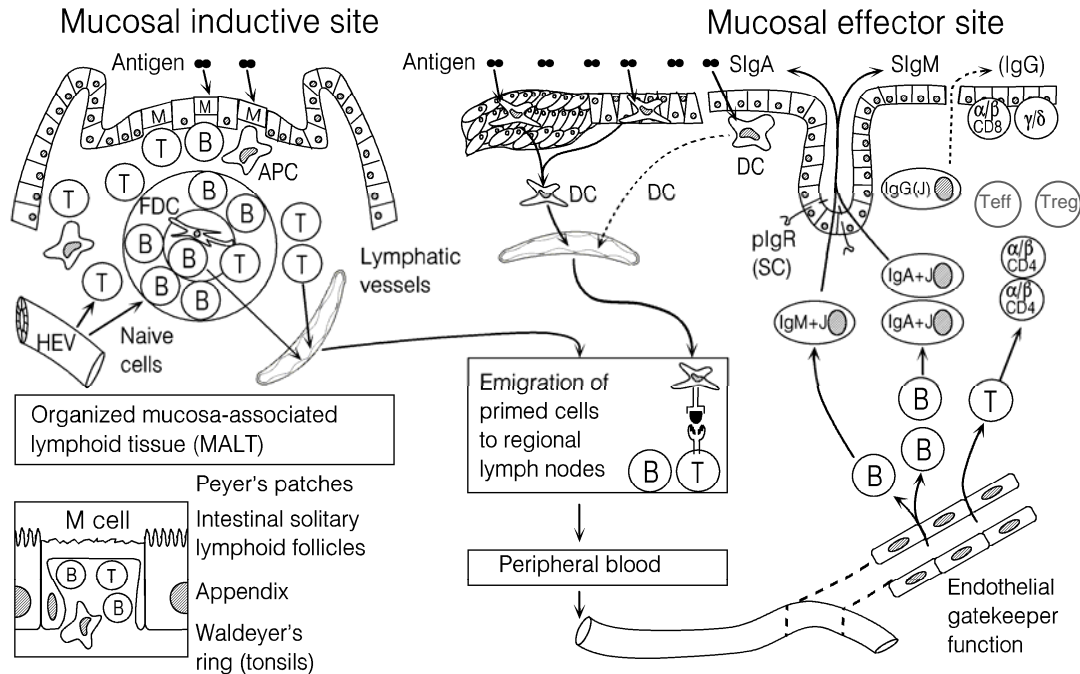


Fig. 3. Schematic depiction of the human mucosal immune system. Inductive sites for mucosal T and B cells are constituted by regional mucosa-associated lymphoid tissue (MALT) with its B-cell follicles and M cell (M)-containing follicle-associated epithelium through which exogenous luminal antigens are actively transported to reach professional antigen-presenting cells (APCs), including dendritic cells (DCs), macrophages, B cells, and follicular dendritic cells. In addition, intra- or subepithelial DCs may capture antigens and migrate via draining lymph to regional lymph nodes where they become active APCs, which stimulate T cells for productive or down-regulatory (suppressive) immune responses. Naïve T and B cells enter MALT (and lymph nodes) via high endothelial venules (HEVs). After priming to become memory/effector T and B cells, they migrate from MALT and regional lymph nodes via lymph and peripheral blood for subsequent extravasation (leakage) at mucosal effector sites. This process is directed by the profile of adhesion molecules and chemokines expressed on the microvasculature, the endothelial cells thus exerting a local gatekeeper function for mucosal immunity. The mucosal lamina propria (effector site) is illustrated with its various immune cells, including B lymphocytes, J chain-expressing IgA and IgM plasma cells, IgG plasma cells with a variable J-chain level (J), and CD4⁺ T cells with effector (Teff) or regulatory (Treg) function. Additional features are the generation of secretory IgA (SIgA) and secretory IgM (SIgM) via pIgR (SC)-mediated epithelial export, as well as paracellular leakage of smaller amounts (broken arrow) of both locally produced and serum-derived IgG antibodies into the lumen. Note that IgG cannot interact with J chain to form a binding site for pIgR. The distribution of intraepithelial lymphocytes (mainly T-cell receptor α/β^+CD8^+ and some γ/δ^+ T cells) also is schematically depicted. The insert (lower left corner) shows details of an M cell and its “pocket” containing various cell types.

Q & A

Q: Dr Brandtzaeg, I think you said that IgA plasma cells probably mature faster in infants in the developing world than in infants in the developed world. Are there studies that show that and show how much faster?

Dr Brandtzaeg: Lars Hanson's group in Sweden has done studies in Pakistan showing more rapidly increasing levels of IgA in secretions than in developed countries. These studies did not involve biopsies and examination of tissue sections, but the amount of IgA in the secretions reflects a more speedy development of the secretory IgA system [Mellander L et al: J Pediatr 1985;107:430-433]. Also, Anne Ferguson found high levels of Escherichia coli LPS antibodies in gut fluid from adults in Dhaka (Bangladesh), while in adults in Edinburgh, gut fluids contained higher levels of antibodies to food antigen [Hoque SS et al: Eur J Gastroenterol Hepatol 2000;12:1185-1193]. So the antigen always will be imprinted on the repertoire of antibodies in the secretor IgA system; it is highly adaptive.

Q: You mentioned that in the small bowel there are between 100 and 250 Peyer's patches. And in the large bowel?

Dr Brandtzaeg: By definition, Peyer's patches contain five to several hundreds of B-cell follicles and are found only in the small intestine, especially in the distal ileum. The number increases until puberty, and then levels off. The large bowel contains numerous solitary or isolated lymphoid follicles, increasing in numbers distally.

Q: Does that mean there are more plasma cells and more immune cells in the large bowel than the small bowel?

Dr Brandtzaeg: No, they are fairly equally distributed, about the same per length unit of the gut. That means that food must have an impact on the development of mucosal immunity in the upper

part of the gut where there are very few or no bacteria. Bacteria are further down in the gut where most of the Peyer's patches and isolated follicles are found. However, antibacterial antibodies could very well be produced in the upper small intestine, as well, because the activated B cells become disseminated, or home, from the GALT system.

Q: You indicated that immune cells in the large bowel do not home to, say, the respiratory tract. Correct?

Dr Brandtzaeg: I think they may spread out from the GALT system to the upper respiratory tract, but we do not see the homing mechanisms that would be required to take memory/effector B cells from the NALT system—for instance, the tonsils—into the small intestinal lamina propria. They may, to some extent, go into the large intestine, but CCR9 must be expressed, and we do not see that to any substantial extent on cells from this area. Thus, the mucosal immune system is integrated but compartmentalized to a remarkable degree, which is very important for mucosal vaccines.