

## Chapter 2

# Mucosal Immunology and Oral Vaccination

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### Introduction

The mucosal surfaces of the gastrointestinal and respiratory tracts represent the principal portals of entry for most infectious agents. Hence, the development of vaccination strategies capable of inducing protective immune responses at the mucosal sites is a priority. Since the mucosal surfaces are exposed to a wide variety of antigens, the mucosal immune system has to discriminate between harmful and harmless inoffensive or beneficial antigens. For this reason, the mucosal immune surfaces are highly regulated by a complex interplay of regulatory mechanisms capable of eliciting strong immune responses against pathogens and protecting the body as well as preventing the induction of strong immune responses against dietary proteins, commensal bacteria, or environmental inoffensive antigens, which can lead to chronic diseases (Mowat 2003; Pabst and Mowat 2012).

Mucosal surfaces are protected from external attacks by physicochemical defense mechanisms comprising innate and adaptive mucosal immune systems. Epithelial barriers on the mucosal surfaces at different sites in the body differ dramatically in their cellular organization, and antigen-sampling strategies at diverse mucosal sites are adapted accordingly. The intestinal mucosa is covered by only a single cell layer (type 1 epithelium), whereas multilayered squamous epithelia line the oral cavity, pharynx, esophagus, and urethra (type 2 epithelium); and the airway and vaginal linings vary from pseudo-stratified to simple epithelium (Box 2.1; Pavot et al. 2012).

A major goal in vaccine design comprises the induction of protective lasting immune responses against potential pathogens on the mucosal surfaces. These responses are most effectively induced by the administration of vaccines onto mucosal surfaces through oral, nasal, rectal, or vaginal routes, when compared with those induced by parenteral routes (Neutra and Kozlowski 2006). In addition, mucosal vaccines offer

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### **Box 2.1 Mucosal Immunity Is Mediated by Different Lines of Defense**

#### **(1) IgA, antimicrobial peptides (such as defensins, angiogenins, defensin-like peptides, and catelicidins released by enterocytes, Paneth cells, as well as by intraepithelial lymphocytes), and mucus glycoproteins**

These components are the first line of defense forming a mucosal layer and dismiss the penetration of most bacteria. IgA neutralizes pathogens while antimicrobial peptides can reach sufficient levels to mediate bacterial lysis in crypts (Mowat 2003).

#### **(2) Epithelial barrier**

The second barrier of defense comprising the monolayer of the epithelial cells (ECs) and the upregulated permeability provided by tight junctions through these cells, which are formed by a single epithelial stem cell; absorptive enterocytes, microbicidal factor-producing Paneth cells, mucus-producing goblet cells, and hormone-producing enteroendocrine cells protect against invasion of luminal microbes into the sterile tissues (Brandtzaeg et al. 1999).

#### **(3) Lamina propria**

It is considered the final barrier before systemic immunity and contains distinct lymphoid structures that can detect and restrain microbes through the action of dendritic cells, macrophages, lymphoid cells, stromal cells, and plasmatic cells (Coombes and Powrie 2008).

needle-free delivery, thereby improving accessibility, safety, and cost-effectiveness. Mucosal vaccines are also advantageous when compared with systemic vaccines from a production and regulatory perspective. For example, vaccines for oral use do not require extensive purification from bacterial by-products since the gut is already heavily populated by bacteria, whereas the same vaccine formulation injected parenterally would have unacceptable endotoxin levels (Lycke 2012). Nevertheless, the vast majority of vaccines in use today are administered by intramuscular or subcutaneous injections, where a proper control on dosage can be accomplished. By contrast, the dose of a mucosal vaccine that enters the body is not accurately determined. Moreover, several challenges to achieve successful mucosal vaccination still prevail, comprising poor induction of mucosal immunity, limited understanding of protective mechanisms and cross talk between mucosal compartments, and the availability of safe and effective mucosal adjuvants as well as delivery systems. Our understanding of mucosal immunity and development of mucosal vaccines has lagged behind, in part because the induction and measurement of mucosal immune responses are more complicated than those elicited by parenteral routes. As a result, only a few mucosal vaccines have been approved for human use worldwide. Among these, oral vaccines against poliovirus, *Salmonella typhi*, *Vibrio cholerae*, and rotavirus, and a nasal vaccine against influenza virus can be mentioned (Pavot et al. 2012; Woodrow et al. 2012). However, research and testing of mucosal vaccines are currently accelerating, stimulated by new information on the mucosal immune system and by the threat of the mucosally transmitted virus, such as the Human

immunodeficiency virus (HIV). Fortunately, current research is providing new insights into the function of mucosal tissues and the interplay of innate and adaptive immune responses that result in immune protection at mucosal surfaces (Neutra and Kozlowski 2006).

To better understand the limitations and challenges for developing successful oral vaccines, some general anatomical and functional characteristics of the mucosal immune system will be described in this chapter, particularly of the one associated with the intestinal mucosa. Current strategies for successful mucosal vaccination will be further analyzed, highlighting the advantages of oral vaccines.

## Organization of the Mucosal Immune System

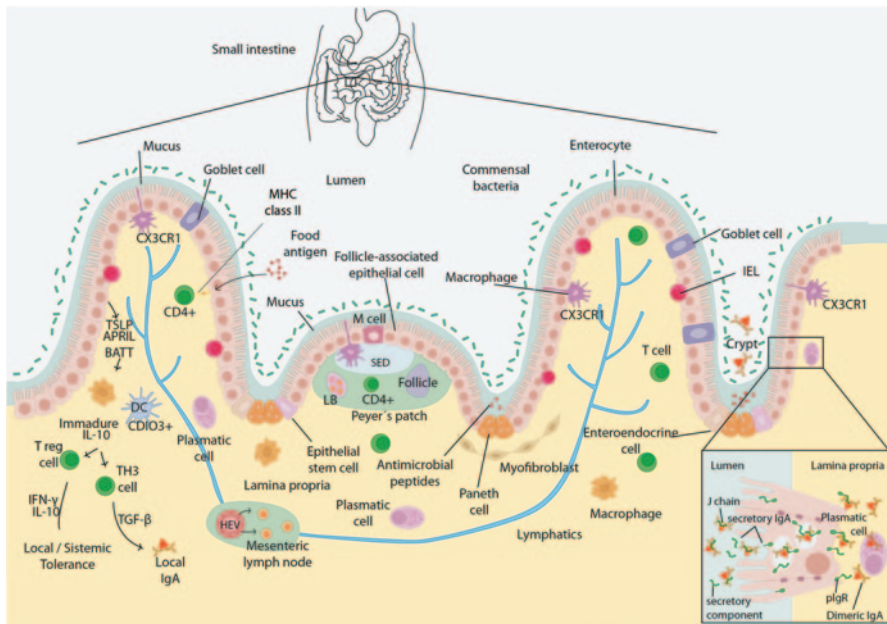
The mucosal immune system can be divided into inductive and effector sites. The first ones are constituted by organized mucosa-associated lymphoid tissue (MALT) as well as mucosa-draining lymph nodes. The latter are represented by the lamina propria (LP), the stroma of exocrine glands, and surface epithelia.

MALT comprises multiple compartments including the gut-associated lymphoid tissue (GALT), which is the largest human mucosa and immunologic organ in the body. The gastrointestinal mucosa is associated to specialized components of the innate and adaptive immunity (specific antigen recognition, effector and memory functions) that protect the host against pathogens, control responses to food components, and mediate tolerance against harmful antigens (Holmgren and Czerkinsky 2005).

In the GALT, the organized tissues responsible for the induction phase of the immune response comprise the Peyer's patches (PP) and mesenteric lymph nodes (MLNs), as well as smaller, isolated lymphoid follicles (ILFs), which have the appearance of microscopic PP and are distributed throughout the walls of the small and the large intestines. The diffuse lymphoid tissue of the effector sites at the intestinal mucosa consists of lymphocytes scattered throughout the epithelium and LP of the mucosa (Fig. 2.1).

## Characteristics of the Organized Inductive Lymphoid Tissues

Organized lymphoid tissues such as the PP consist of collections of large B cell follicles and intervening T cell areas. The lymphoid areas are separated from the intestinal lumen by a single layer of columnar epithelial cells, known as the follicle-associated epithelium (FAE), and a more diffuse area immediately below the epithelium, known as the subepithelial dome (SED; Fig. 2.1). The FAE differs from the epithelium that covers the villus mucosa as it has lower levels of digestive enzymes and a less pronounced brush border, and it is also infiltrated by large numbers of B



**Fig. 2.1** Anatomy and homeostasis of the intestinal immune system. The gut-associated lymphoid tissue (GALT) can be divided into inductive and effector sites, which consist of organized and diffuse lymphoid tissues, respectively. The organized tissues are the Peyer's patches (PP) and mesenteric lymph nodes (MLNs), as well as smaller, isolated lymphoid follicles. The effector tissues consist of lymphocytes scattered throughout the epithelium and lamina propria (LP) of the mucosa. A single layer of intestinal epithelial cells (IECs) provides a physical barrier that separates the commensal bacteria in the intestinal lumen from the underlying LP. The IECs lining the lumen are bathed in nutrients, commensal bacteria, IgA, and goblet cell-produced mucus. These IECs differentiate into villous or colonic enterocytes, which absorb nutrients (small intestine) and water (colon). Progenitor IECs differentiate into both enteroendocrine cells, which secrete enteric hormones, and Paneth cells at the base of the small intestinal crypts. Paneth cell granules contain high concentrations of  $\alpha$ -defensins. Certain subsets of T cells (intraepithelial lymphocytes, IEL) and macrophages cells CX3CR1+ localize between the IECs. In the small intestine, about 80% of IEL are CD8+ lymphocytes and about 70% of CD4+ lymphocytes is present in the LP. The specialized epithelium termed follicle-associated epithelium contains microfold (M) cells that overlie the subepithelial dome (SED) of the organized lymphoid tissue PP consist of a rich zone of B lymphocytes in an area termed follicles, and around them is a thymus-dependent area (TDA), which is rich in CD4+ T lymphocytes. The LP, contains B cells (especially sIgA-producing plasmatic cells), T cells CD4+, stromal cells, and antigen-presenting cells (APCs) such as macrophages and dendritic cells (DCs) CD103+. Oral tolerance is essential to maintain homeostasis. Food proteins and products of commensal bacteria are taken up by IECs which express MHC II, but do not express the costimulatory molecules; thus, they contribute to oral tolerance induction. IECs also produce chemokines like APRIL and B-cell-activating factor (BAFF), which promote B cell recruitment in the LP and class switching in response to TLR signaling, and thymic stromal lymphopoietin (TSLP), the transforming growth factor- $\beta$  (TGF- $\beta$ ), retinoic acid (RA), and possibly other factors that promote the induction of regulatory T (Treg) cells. Specific subsets of intestinal DCs CD103+ express RA-synthesizing enzymes, and in the presence of TGF- $\beta$ , induce the differentiation of naive  $T_R$  cells, Foxp3+. RA also programs DCs to imprint gut-homing properties. These committed  $T_R$  cells home back to the intestinal LP through high endothelial venules (HEVs), where they undergo secondary expansion under the influence of interleukin-10 (IL-10) produced by CX3CR1+ macrophages. These T cells differentiate into Treg cells, and also produce IL-10 and interferon- $\gamma$  (IFN- $\gamma$ ) and/or T helper ( $T_H$ ) 3 cells, which produce TGF- $\beta$ -favoring oral tolerance.

cells, T cells, macrophages, and dendritic cells (DCs). The most notable feature of the FAE is the presence of microfold (M) cells, which are specialized enterocytes that lack surface microvilli and the normal thick layer of mucus. Antigens are taken up by absorptive epithelial cells or specialized epithelial M cells in mucosal inductive sites, or alternatively, can be directly captured by “professional” antigen-presenting cells (APCs), which include DCs, B lymphocytes, and macrophages. Antigen-charged DCs further process and present antigens to T cells located at the interfollicular areas within the PP. Primed lymphocytes exit through the draining lymphatics to the MLNs, where they reside for an undefined period of further differentiation before they migrate into the bloodstream through the thoracic duct and finally accumulate in the mucosa (Holmgren and Czerkinsky 2005; Mowat 2003).

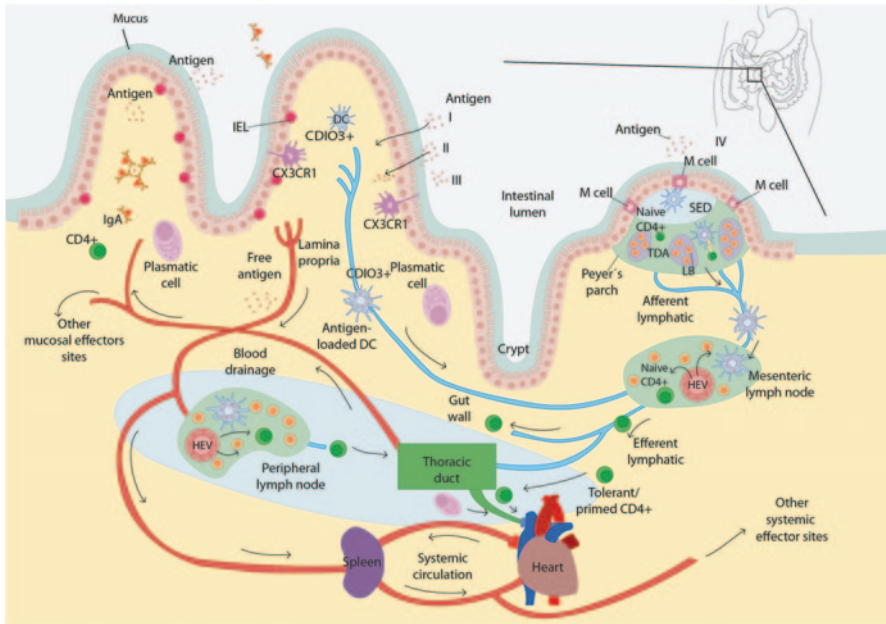
Priming of T and B cells in these inductive tissues and selective homing to mucosal sites lead to either efficient local immune responses or tolerance. However, how the intestinal captured antigens can also induce systemic priming or tolerance involves complex mechanisms. The MLNs are considered alternative sites where T cell priming might occur and explain the induction of local and systemic immunity or tolerance by the oral route. The antigens might reach the MLNs via the draining lymph (Fig. 2.2) or as a result of APCs located in the LP that have taken up antigens either directly from the lumen or from APCs that have acquired unprocessed antigens from M cells, and then migrated to MLNs. T cells that are primed in the MLNs are further differentiated, and then migrate to the mucosa to mediate local immune responses. In addition, since the MLNs can act as a crossover point between the peripheral and systemic immune systems, this pathway might also explain the induction of systemic immunity or tolerance in response to intestinal antigens (Mowat 2003).

## Mucosal Effector Tissues

The diffuse lymphoid tissues are mainly associated with effector responses that are initiated from the organized lymphoid tissues. These diffuse lymphoid tissues are mainly composed of lymphocytes residing as intraepithelial lymphocytes (IELs) in the mucosal epithelium in addition to numerous lymphocytes present in the LP, which is the connective tissue directly underlying the mucosal epithelium.

## Intraepithelial Lymphocytes

The IELs that reside within the epithelium of the intestine form one of the main branches of the immune system by their direct contact with the enterocytes and by their immediate proximity to antigens in the gut lumen. As IELs are located at this critical interface between the core of the body and the outside environment, they must balance protective immunity with an ability to safeguard the integrity of the epithelial barrier, as failure of this function would compromise homeostasis (Cheroutre et al. 2011).



**Fig. 2.2** Antigen uptake in gut-associated lymphoid tissue (GALT). The antigen might enter GALT through different parts of the intestine. Epithelial cells can acquire soluble antigens that have diffused through epithelial tight junctions (*I*) or have been transferred across epithelial cells by transcellular routes (*II*). CX3CR1<sup>+</sup> macrophages can also capture luminal antigens by extending processes through the epithelial layer, and they may pass this to neighboring CD103<sup>+</sup> dendritic cells (DCs) (*III*). Also, the antigen might enter through the microfold (M) cells in the follicle-associated epithelium (FAE) (*IV*) and after transfer to local CD103<sup>+</sup> DCs; the antigen might also gain direct access to the bloodstream from the gut and interact with T cells in peripheral lymphoid tissues. The antigen taken up into Peyer's patches (PP) or lamina propria may enter the bloodstream via the portal vein, first reaching the liver before it becomes distributed into the circulation. Free antigen taken up into afferent intestinal lymph will pass through the mesenteric lymph nodes and eventually enter the bloodstream via the thoracic duct. Once the antigen is sampled by M cells, it is delivered across the epithelial barrier directly to subepithelial DCs that subsequently process and present antigen locally to T cells located at the interfollicular areas within the PP. Alternatively, antigen or antigen-loaded DCs from the PP might gain access to the draining lymph, with subsequent T, B cell recognition in the mesenteric lymph nodes (MLNs). In all cases, the antigen-responsive CD4<sup>+</sup> T cells or plasmatic cells acquire expression of the  $\alpha 4 \beta 7$  integrin and the chemokine receptor CCR9, leave the MLN in the efferent lymph, and, after entering the blood stream through the thoracic duct, exit into the mucosa through the vessels in the LP. T cells and plasmatic cells, which have recognized antigen first in the MLN, may also disseminate from the bloodstream throughout the peripheral immune system. Plasmatic cells produce local sIgA and systemic IgG. Since T cells and plasmatic cells migrate through the circulation, integrin and chemokine signals direct their emigration into tissues. In this manner, imprinted T cells and plasmatic cells have a specific key that allows access to restricted tissues

IELs essentially comprise antigen-experienced T cells belonging to both T cell receptor- $\gamma\delta$  ( $\text{TCR}\gamma\delta$ )<sup>+</sup> and  $\text{TCR}\alpha\beta$ <sup>+</sup> lineages, but are extremely heterogeneous, and the various IEL subsets are distributed differently in the epithelia of the small and large intestines probably influenced by the distinct digestive functions and the physiological conditions between both intestines. In the small intestine, IELs are almost exclusively T cells and include a significant proportion of  $\text{TCR}\gamma\delta$ <sup>+</sup> cells (60%). IELs constitutively express CD103 (also known as the  $\alpha\text{E}$  integrin), which interacts with E-cadherin on intestinal epithelial cells, and most of them, especially in the small intestine, express CD8 $\alpha\alpha$  homodimers, which is a hallmark of their activated phenotype. The majority of IELs express activation markers, such as CD44 and CD69; contain abundant cytoplasmic granules responsible for cytotoxic activity; and can express effector cytokines, such as interferon- $\gamma$  (IFN $\gamma$ ), interleukin-2 (IL-2), IL-4, or IL-17. Furthermore, IELs characteristically express both activating and inhibitory types of innate natural killer (NK) cell receptors, which typify them as stress-sensing (activated) yet highly regulated (resting) immune cells (Cheroutre et al. 2011). IELs play an important role in controlling the entrance of commensal bacteria after epithelial damage via the release of antimicrobial peptides and promoting the repair of injured gut epithelia. IELs express a limited diversity of antigen receptors, keep in a heightened state of activation, and thus avoid the need for a priming step before full activation.

## Lamina Propria Lymphocytes

Lymphocytes in the LP include mainly the CD4<sup>+</sup> T cells and also an important population of plasma cells, which are B lymphocytes that are mainly IgA in type I mucosal tissues like the one present in intestines. An important characteristic of the mucosal adaptive immune response is the local production and secretion of dimeric secretory immunoglobulin A (sIgA), which, unlike other antibody isotypes, are resistant to degradation in the protease-rich external environments of mucosal surfaces. sIgA is secreted as a dimer across the mucosal epithelium by an active transport mechanism using the polymeric Ig receptor (pIgR). sIgA has multiple roles in mucosal defense as it can bind and neutralize pathogens or toxins in the gut despite the presence of active digestive enzymes. It promotes the entrapment of antigens or microorganisms in the mucus preventing direct contact of pathogens with the mucosal surface, a mechanism that is known as “immune exclusion.” Protection of mucosal surfaces by sIgA can also be mediated by intracellular neutralization of pathogens that have invaded the epithelial cells when the sIgA is transported by the pIgR. In addition, antigens can be excreted through the secretion of sIgA joined to the antigens, which is released into the mucosal lumen (Strugnell and Wijburg 2010). Moreover, sIgA-mediated blockade is also a key element in the intestinal homeostasis as it reduces inflammatory activity of the microbiota (Mantis et al. 2011).

Although the adaptive humoral immune defense at mucosal surfaces is mainly mediated by sIgA, locally produced IgM and IgG in the respiratory tract and in the

genitourinary mucosa and serum-derived IgG can also contribute significantly to the mucosal immune defense (Neutra and Kozlowski 2006; Iwasaki 2010).

The lymphocytes that enter the mucosa redistribute into distinct compartments. The functions of mucosal T cells are still largely undefined, but cells with a “memory” or “effector memory” phenotype predominate in both the epithelium and the LP, indicating that these have been exposed to an antigen. In the LP of the intestine, CD4+ T cells are of particular importance in regulating local immune responses. LP CD4+ T cells might be regulatory T (Tregs) cells and therefore responsible for maintaining local tolerance to environmental antigens. These produce large amounts of cytokines, particularly IFN- $\gamma$ , but also IL-4 and IL-10.

LP CD8+ T cells can also have potent cytotoxic T lymphocyte (CTL) activity. Some of these antigen-experienced LP T cells might be true effector cells, and might help local B cells to produce IgA “effector memory” cells, as indicated by the findings supporting that antigen-specific memory CD4+ and CD8+ T cells accumulate preferentially in non-lymphoid tissues, particularly at the intestinal mucosa (Shale et al. 2013; Mowat 2003).

Intestinal CD4+ T cells are essential mediators of immune homeostasis and inflammation. Multiple subsets of CD4+ T cells have been described in the intestine, which represents an important site for the generation and regulation of cells involved in immune responses both within and outside of the gastrointestinal tract. Among intestinal lymphocytes, CD4+ T cells represent a major population implicated in mediating diverse host-protective and homeostatic responses (Shale et al. 2013).

T cell populations can be broadly functionally divided into effector and regulatory populations. The lack of inflammation in the majority of individuals, despite the enormous microbial and antigenic load within the intestine, clearly demonstrates the dominance of regulatory mechanisms in the steady state, condition in which IL-17 cells are the dominant Th17A single positive CD4+ T cells, and preferentially locate the LP of the small intestine and, to a lesser extent, the colon and intestine of adult mice. Interestingly, expansion of Th17 cell populations in the small intestine may occur in the setting of extraintestinal infections or autoimmune diseases without detectable mucosal inflammation. In the steady state, the presence of dominant, suppressive, and regulatory mechanisms restrains innate and adaptive responses. Functionally specialized subsets of CD4+ T cells play an important role in the regulation of intestinal immune responses. The concept of an important functional role for CD4+ Treg cells in maintaining intestinal homeostasis was established originally in mice, where the ability of CD4+ CD25+ Treg cells to prevent disease in the T cell transfer model of colitis was described. A number of subsets of T cells possessing regulatory or suppressive activity have now been characterized, but those expressing the transcription factor Foxp3 and IL-10-producing cells appear to be of particular functional importance in intestinal homeostasis and in the control of inflammation. In comparison with systemic immune compartments, the intestine is enriched with the presence of Treg cells. Although IL-10+ Foxp3+ Treg cells are also found in abundance in the small intestinal LP, a sizable fraction of IL-10+ CD4+ T cells in this location do not express Foxp3, exhibiting a Tr1 phenotype. TGF- $\beta$  plays a critical role in the development and function of Treg cells, including

Foxp3<sup>+</sup> and Tr1 cells. Cells co-expressing ROR $\gamma$ t and Foxp3 are found in intestinal tissues. Notably, both Treg cells and Th17 cells require TGF- $\beta$  for their development, and the presence or absence of further factors, including the STAT3-activating cytokines, IL-6 and IL-23, may determine the balance of these populations in the steady state or inflamed intestine. Interestingly, intestinal CD4<sup>+</sup> T cell subsets are also regulated by environmental factors. The microbiota directs the accumulation of both Treg cells and Th17 cells in the intestinal LP (Shale et al. 2013).

## Intestinal APCs

Together with the epithelial barrier, APCs and IELs are located at the first line of defense. After sensing pathogens, these cellular types release cytokines, antimicrobial peptides, and chemokines as defense or activate and recruit immune cells that furthermore can phagocytose and kill pathogens.

Antigen sampling strategies are adapted to the diverse epithelial barriers that cover mucosal surfaces throughout the body, but all involve collaboration with APCs. Myeloid APCs of the intestine are a heterogeneous population consisting of DCs and macrophages (Pabst and Mowat 2012; Geissman et al. 2010; Scott et al. 2011; Manicassamy and Pulendran 2009). These populations are strategically positioned with the LP and in organized lymphoid structures, and exhibit a number of adaptations associated with their dual role in tolerance and immunity in the intestine. Myeloid APCs might congregate immediately under epithelia, migrate into the epithelial layer, and even extend dendrites into the lumen to capture antigens. DCs can act as a bridge with the adaptive immune system through their ability to acquire antigen in the intestine and migrate to the MLN where they prime the activation of cognate naive T cells. In addition to presenting antigens, intestine-derived DCs are specialized in their ability to prime T cell responses that are focused on the intestine through the upregulation of gut-homing molecules on the responding T cell surface (Box 2.2). At sites of organized mucosal lymphoid tissues, specialized M cells in the lymphoid FAE sample and deliver antigens across the epithelial barrier directly to subepithelial

### Box 2.2 Importance of Mucosal Homing in the Choice of Mucosal Vaccination Route

After the initial exposure to antigen, lymphocytes leave PP or other mucosal inductive sites and migrate into mucosal tissues, including the intestines, lungs, nasal passages, and urogenital tract. These lymphocytes home to the LP or mucosal epithelium where they exert effector activities such as antibody synthesis or killing virally infected cells. The preferential migration of mucosal stimulated lymphocytes to other mucosal sites throughout the body gave rise to the idea of a “common mucosal immune system.” However, it is now apparent that the mucosal immune system is highly compartmentalized

and thus lymphoid responses preferentially migrate into tissues where the response was induced. Therefore, the compartmentalization within the mucosal immune system places constraints on the choice of vaccination route for inducing effective immune responses at the desired sites (Holmgren and Czerkinsky 2005). Therefore, in order to induce and regulate protective immune responses at the appropriate mucosal sites, depending on the invading route of a particular pathogen, it is required to understand the biological basis of the mucosa compartmentalization (Brandtzaeg et al. 1999).

The capacity for selective migration of effector and memory T and B cells back to the original challenge site—the concept of tissue-specific homing—or to the distinct mucosal sites, depends on the differential expression of adhesion molecules on the lymphocyte cell surface as well as on the vascular endothelium. Whereas naive T cells express adhesion molecules and chemokine receptors that restrict their migration mainly (but not entirely) to organized lymphoid tissue, activated memory T cells downregulate these lymphoid-tissue-homing receptors and upregulate tissue-specific adhesion molecules and chemokine receptors that target their migration to non-lymphoid tissues (Kunkel and Butcher 2002).

This imprinting of tissue-homing properties is best described for the gut and skin. Priming of T and B cells in PP and mesenteric lymph nodes preferentially induces the expression of  $\alpha 4\beta 7$  integrin and CC-chemokine receptor 9 (CCR9), whereas T cells that are primed in peripheral lymph nodes upregulate cutaneous leukocyte antigens, CCR4 and CCR10. Endothelial cells of postcapillary venules in the intestinal mucosa constitutively express ligands for  $\alpha 4\beta 7$ -integrin and CCR9, namely mucosal addressin cell-adhesion molecule 1 (MADCAM1) and CC-chemokine ligand 25 (CCL25), also known as thymus-expressed chemokine (TECK), which is expressed selectively by small bowel epithelial cells, allowing lymphoid cells that are induced in intestinal lymphoid tissue to enter this mucosal effector site. Importantly, recent investigations suggest that antigen-presenting DCs process and “interpret” locally produced metabolites to program tissue-specific lymphocyte homing. In the case of GALT, resident DCs metabolize vitamin A to retinoic acid, which stimulates  $\alpha 4\beta 7$ -integrin and CCR9 expression by T cells; and in the skin, local DCs use metabolites of vitamin D3 to program T cells in recurrent laryngeal nerves (RLNs) (Kunkel and Butcher 2002).

The identification of  $\alpha 4\beta 7$ -integrin and CCR9 as mucosal homing receptors interacting with MADCAM1 and CCL25, respectively, was considered the molecular explanation for the fact that mucosal vaccination is required for protection against mucosal infections, whereas parenteral vaccines are generally ineffective to induce mucosal immunity. It must be taken into account that recruitment of lymphoid cells into target tissues requires specific chemokine recognition and adhesion-receptor engagement. The high degree of compartmentalization among the distinct mucosal sites relies on the use of distinct

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An Integrated View

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