PART VII SPECIFIC IMMUNE-MEDIATED DISEASES OF MUCOSAL SURFACES

Overview of the mucosal immune system structure

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Pioneering experiments in the early 1960s showed that the large lymphocytes (lymphoblasts) that enter the bloodstream from the thoracic duct migrate into the intestinal lamina propria and undergo terminal differentiation into plasmablasts and plasma cells. Many of the circulating lymphoblasts express surface IgA (sIgA), and in the gut contain cytoplasmic IgA. These lymphoid cells were thought to be derived mainly from Peyer's patches (PPs), because transfer studies demonstrated that PPs and the draining mesenteric lymph nodes (MLNs), in contrast to peripheral lymph nodes and the spleen, were enriched precursor sources for IgA-producing plasma cells in the gut mucosa. It was also shown that plasma-cell differentiation occurs during dissemination of the mucosal B cells. Thus, the fraction of cells with cytoplasmic IgA increased from an initial 2% in PPs to 50% in MLNs and 75% in thoracic duct lymph, and finally 90% in the intestinal lamina propria.

These seminal studies led to the introduction of the term "IgA cell cycle," and subsequent research showed that B cells bearing other sIg classes than IgA, as well as T cells, when activated in PPs, also exhibit gut-seeking properties. It later became evident that different secretory effector sites can receive activated memory/effector B cells from a variety of mucosa-associated lymphoid tissue (MALT).

This work gave rise to the notion that the mucosal immune system is divided into distinct inductive sites and effector sites. The inductive sites are the organized MALT structures together with mucosa-draining lymph nodes, whereas the effector sites are the mucosal epithelia and the underlying lamina propria, which contains stromal cells and associated connective tissue stroma. The mucosae and related exocrine glands harbor by far the largest activated B-cell system of the body, and the major product—J-chain-containing dimeric IgA together with some pentameric IgM—is immediately

ready for external transport by the polymeric immunoglobulin receptor (pIgR) across the secretory epithelium and into the mucus layers at mucosal surfaces, to provide antibody-mediated immunity (see Chapter 9).

IMMUNE INDUCTIVE LYMPHOID TISSUE

The MALT concept was introduced to emphasize that solitary organized mucosa-associated lymphoid follicles and larger follicle aggregates have common features and are the origin of T and B cells that traffic to secretory effector sites. This functional distinction is important because while the different tissues can be identified and discriminated by histology, single cell suspensions prepared from mucosal surfaces contain a mixture of cells from small MALT structures that cannot be dissected out, and connective tissue. This is particularly a problem in man, because solitary follicles cannot be seen in resected bowel.

1.1 Mucosa-associated lymphoid tissue is different from lamina propria or glandular stroma

MALT is subdivided according to anatomical regions (**Table 1.1**), and the cellular content of these lymphoid structures depends on whether the tissue is normal or chronically inflamed, superimposed upon striking age and species differences (**Figure 1.1**). The PPs in the distal small intestine of humans, rodents, and rabbits are classical MALT structures. PPs are inductive compartments generating conventional (B-2) sIgA-expressing memory/effector B cells and T cells, which, after a journey through lymph and peripheral blood, enter the gut mucosa. This "homing" appears to be antigen independent, but local antigens penetrating into the lamina propria contribute to local retention, proliferation, and differentiation of the extravasated lymphoid cells. Thus, although the lamina propria is considered an effector site, it is clearly important for the expansion and terminal differentiation of T and B cells. Some expansion of mucosal memory/effector T cells can also occur in the mucosal surface epithelium, and there is considerable "cross talk" between these two effector compartments.

TABLE 1.1 DIFFERENT REGIONS OF MALT AND THEIR COMPONENTS

Region	Components
GALT (Gut-associated lymphoid tissue)	Peyer's patches (PPs) and isolated lymphoid follicles constitute the major part of GALT, but also the appendix is included.
NALT (Nasopharynx-associated lymphoid tissue) and tonsils	Rodents lack tonsils but do have paired NALT structures dorsally in the floor of the nasal cavity.
	In humans, tonsils consist of the lymphoid tissue of Waldeyer's pharyngeal ring, including the adenoids (the unpaired nasopharyngeal tonsil) and the paired palatine tonsils. Scattered isolated lymphoid follicles may also occur in nasal mucosa (NALT).
BALT (Bronchus-associated lymphoid tissue)	Not generally detectable in normal lungs of adult humans.