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## **Terminology / Terminologie**

### **Nomenclature of mucosa-associated lymphoid tissue**

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**[IUIS/WHO Subcommittee on MALT Nomenclature]**

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## **Summary**

*The main inductive sites for mucosal immunity are organized lymphoid tissue structures covered by a specialized epithelium that exploits various biological mechanisms for uptake and inward transport of exogenous antigens. From such mucosa-associated lymphoid tissue (MALT), primed memory/effector immune cells home to various effector tissues. The complexity of the mucosal immune system necessitates that immunologists in this field adopt precise terminology as a crucial means of communication. In this article abbreviations are defined for discrete mucosal immune-cell compartments, belonging to, and beyond, the MALT structures.*

## **Background and definitions**

Until recently, there was no consensus as to how various tissue compartments involved in mucosal immunity should be named and classified. This lack of standardized terminology was confusing for newcomers joining the field. To address this issue, the Nomenclature Committee of the Society for Mucosal Immunology (SMI) under its chair Michael W. Russell, recommended adoption of a standard nomenclature of these compartments, as initially proposed by Per Brandtzaeg and Reinhard Pabst in 2004 (1). This terminology was unanimously approved by the General Assembly of the Society for Mucosal Immunology (SMI) at the 13<sup>th</sup> ICMI in Tokyo,

2007. The nomenclature is now formally recognized by the IUIS/WHO Nomenclature Committee.

The major effector arm of mucosal immunity is the secretory Ig system. The terminology of its effector molecules was approved by SMI in 1997 and also by the IUIS/WHO Nomenclature Committee (2). The awareness and proper use of this nomenclature has been important to eliminate confusion in the scientific literature, but problems still remain. Readers are therefore referred to an update of this terminology in an article where also the recommended nomenclature for mucosal immune-cell compartments is delineated in greater detail (3). The proposed terminology is in harmony with functional specialization of the various compartments as well as with classical concepts of histology.

The major inductive sites for mucosal immunity are constituted by organized mucosa-associated lymphoid tissue (MALT) as well as local/regional mucosa-draining lymph nodes (LNs), whereas the effector sites consist of distinctly different histological compartments – including the lamina propria (LP) of various mucosae, the stroma of exocrine glands, and surface epithelia (1, 3). It should be noted, however, that although the LP is considered an effector site, it is still important for the expansion of B cells and their terminal differentiation to plasma cells.

### **Recommended nomenclature for MALT and other mucosal immune-cell compartments**

Peyer's patches (PPs) in the small intestine of humans, rodents and rabbits are typical MALT structures. The definition of MALT was originally based on mouse repopulation experiments in which B cells were obtained from bronchus-associated lymphoid tissue (BALT) and PPs as well

as the surrounding LP (4). MALT structures lack afferent lymphatics and sample exogenous antigens directly from the mucosal surfaces through a characteristic follicle-associated epithelium (FAE) containing “microfold” or “membrane” (M) cells (1, 3). These specialized thin epithelial cells effectively transfer soluble and especially particulate antigens such as microorganisms from the gut lumen to the underlying lymphoid tissue.

MALT structures are sub-divided according to their anatomical location (Table 1), and their distribution and composition vary considerably among different species (1). Also the age and tissue state (normal or chronically inflamed) have an impact on the appearance of MALT. In contrast to PPs and tonsils, other human MALT structures apparently do not develop prenatally (1), and their occurrence and size generally depend on induction by exogenous stimuli. For instance, BALM is not regularly found in normal lungs of adults (1, 3).

Gut-associated lymphoid tissue (GALT) comprises PPs, the appendix, and isolated lymphoid follicles (ILFs), which all are considered inductive sites for mucosal B and T cells. Early animal studies demonstrated that also mesenteric LNs (MLNs) are enriched precursor sources for intestinal IgA-producing plasma cells (5, 6). The proportion of B cells containing cytoplasmic IgA was found to increase from PPs to MLNs and the thoracic duct lymph, and finally to the intestinal LP because of terminal differentiation into plasma cells. These seminal findings gave rise to the term “IgA cell cycle”. Later studies have demonstrated that T cells as well as B cells expressing other isotypes than IgA, but induced in PPs, also exhibit gut-seeking properties (7).

Small-intestinal ILFs have best been characterized immunologically in mice, showing functional features compatible with induction of local IgA responses (1, 3). Colonic ILFs are morphologically more heterogeneous, sometimes penetrating the muscularis mucosae, especially

in the presence of inflammation. In humans, such irregular "basal lymphoid aggregates" are much more frequent in ulcerative colitis and Crohn's disease than in the healthy large bowel, but they probably have the same functional nature as normal colonic ILFs (8).

## **Comments on the MALT concept**

GALT is the largest and best defined part of MALT, but additional potentially inductive sites for mucosal B cells are associated with the oro- and naso-pharynx, such as the tonsils in humans. Rodents lack tonsils but paired MALT structures occur on both sides of the nasopharyngeal duct dorsal to the cartilaginous soft palate (9). These structures were originally referred to as NALT, or "nasal-associated lymphoid tissue". This is grammatically incorrect, and some authors have therefore changed it to "nose-associated lymphoid tissue". We recommend, instead, "nasopharynx-associated lymphoid tissue", which in humans would comprise the unpaired nasopharyngeal tonsil (also called "adenoids" – note, in plural), the paired palatine tonsils and other smaller lymphoid structures of Waldeyer's pharyngeal ring.

Some mucosal immunologists have introduced the term 'organized MALT' (O-MALT) for the proper MALT structures, while "diffuse MALT" (D-MALT) refers to effector compartments such as the LP and surface epithelium. We strongly recommend that these terms be abandoned because they are in direct conflict with the classical definition of a lymphoid tissue.

Moreover, we discourage referring to the mucosal immune system as the "common mucosal immune system" (CMIS) – a term originally introduced to emphasize the dynamic cell migration that integrates various inductive sites and distant effector sites (4). Although this term has been valuable in establishing the concept of local immunity as distinct from the systemic

counterpart, it is now clear that striking compartmentalization exists in the homing cues for the migration of memory B and T cells to different mucosal effector tissues (7, 9). Thus, there is no uniform (“common”) integration of mucosal immunity throughout the body.

Finally, despite the fact that mucosal immune responses are amplified in mucosa-draining local/regional LNs, they should not be included in the MALT concept. Thus, although partly involved in the intestinal immune system, MLNs are not true GALT structures because they do not sample antigens directly from the lumen via M cells. Likewise, although it may be appropriate to refer to head-and-neck-draining LNs as part of the mucosal immune system, we recommend to replace the acronym CONALT (for cranial-, oral-, and nasal-associated lymphoid tissue) with cervical LNs (CLNs), defining them further as “deep” or “superficial”.

Several other potential MALT structures have been named in the literature, including: SALT/DALT (salivary-gland- or duct-associated lymphoid tissue); CALT (conjunctiva-associated lymphoid tissue); LDALT (lacrimal-drainage-associated lymphoid tissue); TALT (Eustachian tube-associated lymphoid tissue); and LALT (larynx-associated lymphoid tissue). Their putative immune-inductive function needs better characterization.

## References

1. Brandtzaeg P, Pabst R. Let’s go mucosal: communication on slippery ground. *Trends Immunol*, 2004, **25**: 570-577.
2. Turner MW, Russell MW, Gleeson M, Brandtzaeg P, Ferguson A, Hanson LÅ, Lamm ME, Mestecky J, Moro I, Underdown BJ, Vaerman JP, and IUIS/WHO Subcommittee on IgA Nomenclature. Terminology: Nomenclature of immunoglobulin A and other proteins of the mucosal immune system. *Bull Wld Health Org*, 1998, **76**: 427-428.
3. Brandtzaeg P, Kiyono H, Pabst R, Russell MW. Terminology: Nomenclature of mucosa-associated lymphoid tissue. *Mucosal Immunol*, 2008, **1**: 31-37.
4. McDermott MR, Bienenstock J. Evidence for a common mucosal immunologic system. I. Migration of B immunoblasts into intestinal, respiratory, and genital tissues. *J Immunol*, 1979, **122**: 1892-1898.

5. Craig SW, Cebra JJ. Peyer's patches: an enriched source of precursors for IgA-producing immunocytes in the rabbit. *J Exp Med*, 1971, **134**: 188-200.
6. McWilliams M. *et al.* Mesenteric lymph node B lymphoblasts which home to the small intestine are precommitted to IgA synthesis. *J Exp Med*, 1977, **145**: 866-875.
7. Brandtzaeg P, Johansen F-E. Mucosal B cells: phenotypic characteristics, transcriptional regulation, and homing properties. *Immunol Rev*, 2005, **206**: 32-63.
8. Carlsen HS, Baekkevold ES, Johansen FE, Haraldsen G, Brandtzaeg P. B cell attracting chemokine 1 (CXCL13) and its receptor CXCR5 are expressed in normal and aberrant gut associated lymphoid tissue. *Gut*, 2002, **51**: 364-371.
9. Kiyono H, Fukuyama S. NALT- versus Peyer's-patch-mediated mucosal immunity. *Nat Rev Immunol*, 2004, **4**: 699-710.

Table 1: **Recommended nomenclature for mucosa-associated immune-cell compartments**

<b>Recommended abbreviations</b>	<b>Explanations</b>
<b>LP</b>	Lamina propria Refers usually to the connective tissue of gut mucosa, restricted to the stroma above the muscularis mucosae (thus excluding the submucosa), but can also be used in relation to other mucosae
<b>IEL compartment</b>	Surface epithelium Refers usually to the epithelium of the small intestine where most IELs occur
<b>FAE</b>	Follicle-associated epithelium Covers the domes of MALT structures and contains variable numbers of M cells
<b>MALT</b>	Mucosa-associated lymphoid tissue The principal inductive sites for mucosal immune responses, subdivided according to anatomical location as below
GALT	Gut-associated lymphoid tissue
PP	Peyer's patch
ILF	Isolated (solitary) lymphoid follicle PPs and ILFs constitute the major part of GALT, but also the appendix is included although functionally less explored
NALT	Nasopharynx- or nose-associated lymphoid tissue In humans, NALT consists of the lymphoid tissue of Waldeyer's pharyngeal ring, including the adenoids (the unpaired nasopharyngeal tonsil) and the paired palatine tonsils. Rodents lack tonsils, but do have paired NALT structures dorsally in the floor of the nasal cavity
BALT	Bronchus-associated lymphoid tissue Not generally present in normal lungs of adult humans
<b>MLN</b>	Mesenteric lymph node
<b>CLN</b>	Cervical lymph node Should be specified as deep or superficial