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# Terminology: nomenclature of mucosa-associated lymphoid tissue

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Stimulation of mucosal immunity has great potential in vaccinology and immunotherapy. However, the mucosal immune system is more complex than the systemic counterpart, both in terms of anatomy (inductive and effector tissues) and effectors (cells and molecules). Therefore, immunologists entering this field need a precise terminology as a crucial means of communication. Abbreviations for mucosal immune-function molecules related to the secretory immunoglobulin A system were defined by the Society for Mucosal Immunology Nomenclature Committee in 1997, and are briefly recapitulated in this article. In addition, we recommend and justify standard nomenclature and abbreviations for discrete mucosal immune-cell compartments, belonging to, and beyond, mucosa-associated lymphoid tissue.

## INTRODUCTION

It is instructive to categorize various tissue compartments involved in mucosal immunity according to their main function. However, until recently, there was no consensus in the scientific community as to how these compartments should be named and classified. This lack of standardized terminology has been particularly confusing for newcomers to the mucosal immunology field. To address this issue, the Nomenclature Committee of the Society for Mucosal Immunology, under its chair Michael W. Russell, recommended adoption of a standard nomenclature initially proposed by Brandtzaeg and Pabst in 2004.<sup>1</sup> This terminology was unanimously approved by the Society for Mucosal Immunology's General Assembly at the 13th ICMI in Tokyo, 2007.

This paper delineates this recommended nomenclature, with the primary aim of improving communication about the anatomy of the mucosal immune system. Before addressing this recommendation, however, we would like to recapitulate the previously proposed nomenclature for molecules related to the secretory immunoglobulin A (SIgA or S-IgA) system. This seems to be necessary as the proper terminology is often neglected by many immunologists—and even by many major journals of immunology.

## RECOMMENDED NOMENCLATURE FOR SECRETORY IMMUNE-FUNCTION MOLECULES

The molecular specialization of the SIgA system was described as early as in 1965,<sup>2</sup> and a common epithelial transport model

for dimers (and larger polymers) of IgA and pentamers of IgM was proposed in 1974.<sup>3,4</sup> The epithelial glycoprotein designated secretory component (SC) by WHO in 1972 (previously called “transport piece” or “secretory piece”) turned out to be responsible for the receptor-mediated transcytosis of J-chain-containing Ig polymers (pIgs) through secretory epithelia,<sup>5</sup> and the functional name polymeric Ig receptor (pIgR) is now commonly used for the transmembrane form of SC. During export of pIgs, the cleaved ectodomain of the pIgR is incorporated into SIgA and secretory IgM as the so-called bound SC, which stabilizes particularly SIgA by covalent bonding, or is released from unoccupied receptor into secretions as free SC. Bound and free SC can be distinguished by conformational epitopes<sup>6</sup> and may in different ways exhibit innate immune functions.<sup>7</sup> SC thus exists in three forms with distinct functional roles.

The terminology of the SIg system (**Table 1**) was approved by the Society for Mucosal Immunology in 1997 and also by the IUIS/WHO Nomenclature Committee.<sup>8</sup> The awareness and proper use of this nomenclature will be important for eliminating confusion when discussing this system, examples of which are the still common use of a small “s” (which stands for “surface”) as prefix for the SIgs, and the often neglected specification of SC as being either bound or free in distinction from membrane SC.

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Received 2 October 2007; accepted 3 October 2007. doi:10.1038/mi.2007.9

**Table 1 Recommended nomenclature for secretory immune-function molecules<sup>a</sup>**

Preferred abbreviations	Explanations
SIgA (or S-IgA)	Secretory IgA
SIgM (or S-IgM)	Secretory IgM
pIgA	Polymeric IgA
	Refers mainly to dimers but also includes larger polymers of J-chain-containing IgA
J chain	Joining chain
SC	Secretory component
	Exists in three forms: membrane SC; bound SC; and free SC
pIgR	Polymeric Ig receptor
	The same as membrane SC

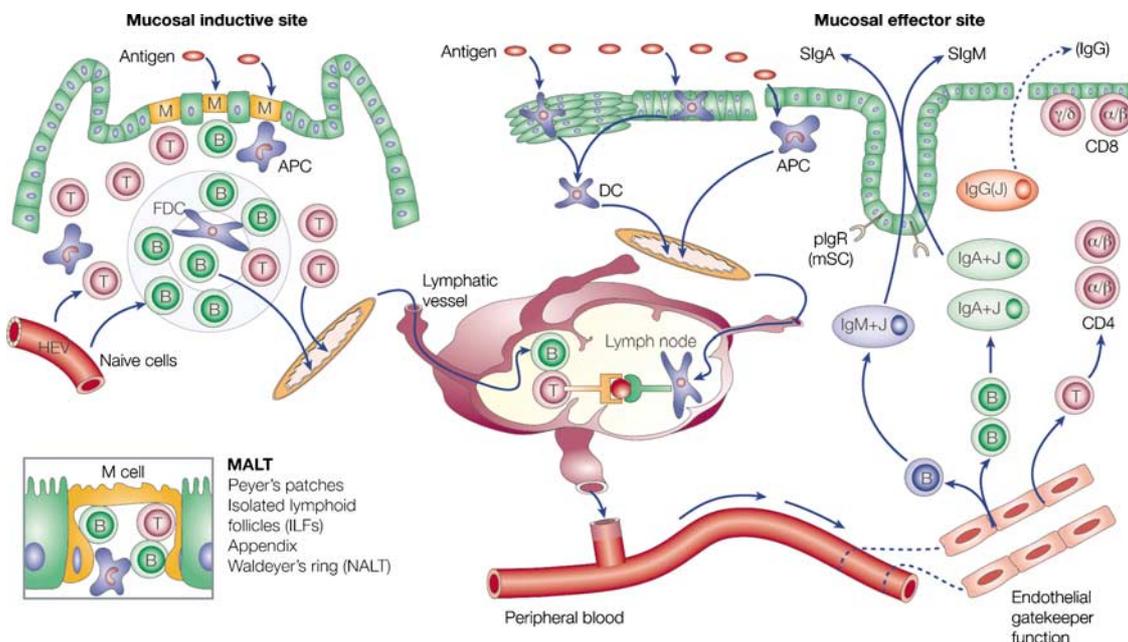
pIgA, IgA dimers/polymers; pIgR, polymeric Ig receptor; SC, secretory component; SIgA, secretory immunoglobulin A; SIgM, secretory immunoglobulin M.  
<sup>a</sup>Approved by IUIS/WHO Subcommittee on IgA nomenclature.<sup>8</sup>

**RECOMMENDED NOMENCLATURE FOR MUCOSA-ASSOCIATED IMMUNE-CELL COMPARTMENTS**

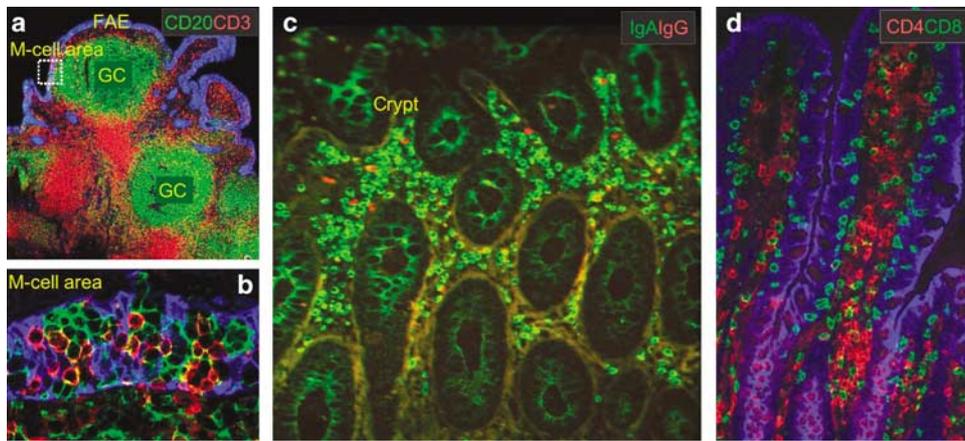
**Inductive and effector tissues**

No attempt has been made previously to standardize the terminology applicable to the various tissue compartments involved in the mucosal immune system. These compartments can principally be divided into inductive sites—where antigens sampled from mucosal surfaces stimulate cognate naive T and B lymphocytes—and effector sites—where the effector cells after extravasation, retention, and differentiation perform their action, for instance by contributing to the formation of SIgA antibodies (Figures 1 and 2).

The 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.<sup>1</sup> Peyer's patches (PPs) in the small intestine of humans, rodents, and rabbits are typical MALT structures believed to be a main



**Figure 1** Depiction of the human mucosal immune system. Inductive sites for mucosal immunity are constituted by regional MALT with their B-cell follicles and M-cell (M)-containing follicle-associated epithelium through which exogenous antigens are transported actively to reach APCs, including DCs, macrophages, B cells, and FDCs. In addition, quiescent intra- or subepithelial DCs may capture antigens at the effector site (exemplified by nasal mucosa in the middle) and migrate via draining lymphatics to local/regional lymph nodes where they become active APCs, which stimulate T cells for productive or downregulatory (suppressive) immune responses. Naive B and T cells enter MALT (and lymph nodes) via HEVs. After being primed to become memory/effector B and T cells, they migrate from MALT and lymph nodes to peripheral blood for subsequent extravasation at mucosal effector sites (exemplified by gut mucosa on the right). This process is directed by the local profile of vascular adhesion molecules and chemokines, the endothelial cells thus exerting a local gatekeeper function for mucosal immunity. The gut lamina propria contains few B lymphocytes but many J-chain-expressing IgA (dimers/polymers) and IgM (pentamers) plasmablasts and plasma cells. Also, there are normally some rare IgG plasma cells with a variable J-chain level (J), and many T cells (mainly CD4<sup>+</sup>). Additional features are the generation of SIgA and SIgM via pIgR (mSC)-mediated epithelial transport, as well as paracellular leakage of smaller amounts (broken arrow) of both locally produced and plasma-derived IgG antibodies into the lumen. There may also be some active transport of IgG mediated by the neonatal Fc receptor (not indicated). Note that IgG cannot interact with J chain to form a binding site for pIgR. The distribution of intraepithelial lymphocytes (mainly T-cell receptor  $\alpha/\beta^+$ CD8<sup>+</sup> and some  $\gamma/\delta^+$  T cells) is also depicted. The inset (lower left corner) shows details of an M cell and its "pocket" containing various cell types. The cartoon is modified from Brandtzaeg and Pabst<sup>1</sup> with permission from Elsevier. APCs, antigen-presenting cells; DCs, dendritic cells; FDCs, follicular dendritic cells; HEVs, high endothelial venules; MALT, mucosa-associated lymphoid tissue; mSC, membrane secretory component; pIgR, polymeric Ig receptor; SIgA, secretory IgA; SIgM, secretory IgM.



**Figure 2** Illustration of three mucosal immune-cell compartments. (a,b) Three-color immunofluorescence staining of B cells (CD20, green), T cells (CD3, red), and epithelium (cytokeratin, blue) in cryosection of human Peyer's patch. (b) Details from the M-cell areas framed on the left in the follicle-associated epithelium (a) covering a B-cell follicle. (c) Two-color immunofluorescence staining for IgA (green) and IgG (red) in a section from normal human large bowel mucosa. Crypt epithelium shows selective transport of IgA, and only a few scattered IgG-producing cells are seen in the lamina propria together with numerous IgA plasma cells. (d) Three-color immunofluorescence staining for CD4<sup>+</sup> (red) and CD8<sup>+</sup> (green) T cells in normal human duodenal mucosa. The epithelium of the villi is blue (cytokeratin). Note that most of the elements with weak CD4 expression seen in the background are either macrophages or dendritic cells. The immunofluorescence pictures are original images from the Brandtzaeg laboratory, reproduced from Brandtzaeg and Pabst<sup>1</sup> with permission from Elsevier.

source of conventional (B2) surface (s)IgA-expressing primed (memory/effector) and class-switched mucosal B cells.<sup>9,10</sup>

The term MALT was first coined to emphasize that solitary organized mucosa-associated B-cell follicles and larger lymphoid aggregates have common features and are the origin of cells that traffic to mucosal effector sites.<sup>11</sup> MALT is sub-divided according to anatomical regions (Table 2), and the distribution and composition of such lymphoid structures vary considerably with species (Figure 3). 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 do not apparently develop prenatally,<sup>1</sup> and their occurrence and size generally depend on induction by exogenous stimuli. For instance, bronchus-associated lymphoid tissue (BALT) is not regularly found in normal lungs of adults—reportedly being absent also in 60% of healthy adolescents and children.<sup>12</sup>

It should be noted that although LP is considered an effector site, it is still important for the expansion of B cells and their terminal differentiation to plasma cells (PCs).<sup>9</sup> In addition, T-cell-independent switch of B cells to IgA expression has been reported to occur in murine LP.<sup>10</sup> This event may particularly involve the large contingent of B1 cells derived from the peritoneal cavity in mice—a possibility that remains controversial, however, because of discrepant findings.<sup>1,13</sup> No evidence exists to suggest that B1 cells populate significantly human gut mucosa,<sup>1,9</sup> and no convincing signs of class switch to IgA have previously been found in normal human intestinal LP.<sup>14</sup> Nevertheless, in the large bowel, bacteria could induce switch factors in epithelial cells and LP dendritic cells (DCs) that may drive T-cell-independent B-cell development toward the IgA2 subclass.<sup>15</sup> The first evidence for such a role of the gut microbiota was obtained as early as in 1995 by showing that jejunal segments with bacterial

overgrowth had an ~50% reduction of the IgA1:IgA2 mucosal PC ratio.<sup>16</sup>

Finally, expansion of memory/effector T cells can apparently take place within the surface epithelium, which is often referred to as the intraepithelial lymphocyte (IEL) compartment (Table 2). There is considerable “cross talk” both within and between the LP and IEL compartments.<sup>17</sup>

### The MALT concept

The concept of MALT was originally based on mouse repopulation experiments with B cells obtained from BALT and PPs as well as the surrounding LP.<sup>11</sup> Notably, all MALT structures resemble LNs—with variable T-cell zones intervening between the B-cell follicles—and contain a variety of antigen-presenting cells, including DCs and macrophages. However, MALT lacks afferent lymphatics because all such lymphoid structures actively sample exogenous antigens directly from the mucosal surfaces through a characteristic follicle-associated epithelium containing “microfold” or “membrane” (M) cells.<sup>1</sup> These specialized thin epithelial cells effectively transfer soluble and especially particulate antigens such as microorganisms from the gut lumen.<sup>18</sup>

Gut-associated lymphoid tissue (GALT) comprises PPs, the appendix, and isolated lymphoid follicles (ILFs), which are considered inductive sites for mucosal B and T cells. The occurrence of other GALT-like elements such as lymphocyte-filled villi and cryptopatches is species-dependent (Figure 3), and these structures do not appear to be involved in B-cell induction.<sup>1</sup> In fact, no conclusive immunological function has been identified for the extremely rare T-cell-dominated human lymphocyte-filled villi;<sup>19</sup> and although cryptopatches were originally thought to be the origin of IELs in mice,<sup>20</sup> more recent data have questioned this notion and provided evidence to suggest that IELs are thymus-dependent even in this species.<sup>21</sup> These small lymphoid structures may instead, represent precursors of marine ILFs.<sup>22</sup>

**Table 2 Recommended nomenclature for mucosa-associated immune-cell compartments**

Preferred abbreviations	Explanations
LP	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
IEL compartment	Surface epithelium Refers usually to the epithelium of the small intestine where most intraepithelial lymphocytes (IELs) occur
FAE	Follicle-associated epithelium Covers the domes of MALT structures and contains variable numbers of M cells
MALT	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 have paired NALT structures dorsally in the floor of the nasal cavity
BALT	Bronchus-associated lymphoid tissue Not generally present in the normal lungs of adult humans
MLN	Mesenteric lymph node
CLN	Cervical lymph node Should be specified as deep or superficial

More details can be found in ref.1

Early animal studies demonstrated that not only PPs, but also mesenteric LNs (MLNs) are enriched precursor sources for intestinal IgA-producing PCs.<sup>23,24</sup> Differentiation of sIgA<sup>+</sup> B cells takes place during their dispersion to the effector sites.<sup>25,26</sup> Thus, the differentiated fraction of B cells with cytoplasmic IgA was only 2% in PPs but increased to 50% in MLNs, 75% in thoracic duct lymph, and finally 90% in the intestinal LP because of terminal maturation to PCs.<sup>27</sup> Such seminal findings gave rise to the term "IgA cell cycle."<sup>28</sup> In humans, a clonal relationship between sIgA<sup>+</sup> B cells in PPs and IgA-producing PCs in LP provides strong support for this notion.<sup>29</sup> 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.<sup>9</sup>

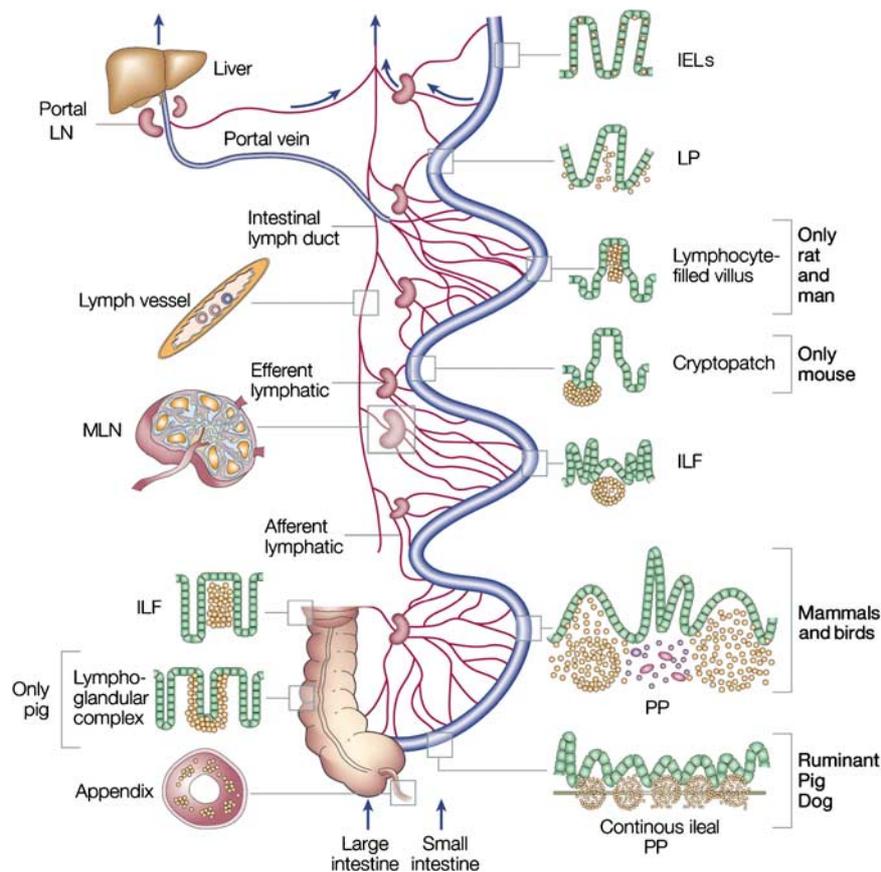
#### Distribution of GALT structures

Human PPs occur mainly in the distal ileum and contain by definition between 5 and 200 aggregated lymphoid follicles.<sup>30</sup> Human PP *anlagen*, composed of CD4<sup>+</sup> DCs, can be seen at 11 weeks of gestation, and discrete T- and B-cell areas occur at 19 weeks. However, no germinal centers appear until shortly after birth, reflecting dependency on antigenic stimulation which in childhood also induces some follicular

hyperplasia, facilitating the macroscopic visibility of PPs.<sup>31</sup> Thus, the number of macroscopically identifiable human PPs increases from some 50 at the beginning of the last trimester to 100 at birth and 250 in the midteens, then diminishes to become approximately 100 between 70 and 95 years of age.<sup>30</sup>

In addition, the human gut harbors at least 30,000 ILFs, increasing in density distally.<sup>32</sup> The normal small intestine contains on average only 1 follicle per 269 villi in the jejunum but one per 28 villi in the ileum;<sup>19</sup> in the normal large bowel, the density of ILFs as seen in tissue sections increases from 0.02 per mm length unit of muscularis mucosae in the ascending colon to 0.06 per mm in the rectosigmoid.<sup>33</sup>

Small-intestinal ILFs have best been characterized immunologically in mice, showing functional features compatible with induction of local IgA responses.<sup>34</sup> Colonic ILFs are morphologically more heterogeneous, sometimes penetrating the muscularis mucosae, especially in the presence of inflammation.<sup>35</sup> 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.<sup>36</sup>



**Figure 3** Delineation of lymphoid-cell distribution in various compartments of the gut wall with some species differences indicated. Lymphocytes can leave the gut wall via draining lymphatics afferent to mesenteric lymph nodes (MLNs), or via portal blood reaching the liver where important regulation of immunity apparently takes place, particularly induction of tolerance. Commonly used abbreviations (see Table 2) are shown for various aggregates of lymphoid cells such as Peyer's patches (PPs). The frequency of M cells (not indicated see Fig. 1) in the follicle-associated epithelium of PPs is highly variable among different species, and a reliable marker for these specialized epithelial cells has not been identified in humans. Note also that, in contrast to the antigen-dependent priming of B cells that takes place in PPs of mammals and birds, the continuous ileal PP present in ruminants, pigs, and dogs appears to be a primary lymphoid organ responsible for antigen-independent B-cell development, similar to the bursa of Fabricius in chicken (not indicated). This PP can be up to 2 m long and constitute 80–90% of the intestinal lymphoid tissue. Reptiles and fish do not have PPs. In these species, the gut immune system is composed of leukocytes scattered in the epithelium and occasional small non-organized lymphoid aggregates. (Modified from Brandtzaeg and Pabst<sup>1</sup> with permission from Elsevier.)

### PERSISTENT CONFUSION ABOUT THE MALT CONCEPT

Although GALT is the largest and the best-defined part of MALT, additional potentially inductive sites for mucosal B cells are regularly associated with the oro- and nasopharynx, such as the tonsils in humans. Interestingly, the cellular-molecular mechanisms involved in the organogenesis of various MALT structures show both similarities and still unexplained quite intriguing differences.<sup>1,35–39</sup>

Rodents lack tonsils but paired MALT structures occur on both sides of the nasopharyngeal duct dorsal to the cartilaginous soft palate.<sup>40</sup> These structures were originally referred to as NALT or “nasal-associated lymphoid tissue.”<sup>40</sup> Grammatically, this is a misnomer, and some authors have therefore changed it to “nose-associated lymphoid tissue.” We recommend, instead, “nasopharynx-associated lymphoid tissue,” which in humans comprises the unpaired nasopharyngeal tonsil (also called “adenoids”—note, in plural), the paired palatine tonsils, and other smaller lymphoid structures of Waldeyer's pharyngeal ring.<sup>41,42</sup>

As mentioned above, the functional distinction between inductive and effector sites is not absolute,<sup>9</sup> but the cues for extravasation, migration, and accumulation of naive vs. memory/effector B and T cells within these immune compartments are nevertheless different.<sup>7,38,43,44</sup> It is therefore confusing when authors even in major journals and textbooks refer to mucosal effector compartments and their cells (e.g., LP lymphocytes and IELs) as part of MALT. This is in direct conflict with the classical definition of a lymphoid tissue as stated in authoritative texts such as *Terminologia Anatomica* (International Anatomical Terminology).<sup>45</sup>

*Gray's Anatomy*—in an attempt at clarification—further confuses the issue;<sup>46</sup> this text introduces the term “organized MALT” (O-MALT) for the proper MALT structures, while “diffuse MALT” (D-MALT) refers to “the disseminated population of lymphocytes within the LP and epithelial base.” Although we are aware of the fact that some mucosal immunologists have used these terms, we strongly recommend that they be abandoned. Moreover, we discourage referring to the “common”

mucosal immune system—a term that originally was introduced to highlight the integration between various inductive sites and separate effector sites.<sup>11</sup> Although this notion has been operationally quite useful, the term now confuses this issue because recent work has revealed striking compartmentalization in the homing cues for memory/effector cells migrating to different mucosal tissues.<sup>7,9,38,44</sup>

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 being part of the intestinal immune system, MLNs should not be called GALT structures. This distinction is important to emphasize the fact that MALT samples antigens directly from the lumen via M cells.<sup>18</sup> 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). However, it is necessary to specify the CLNs as being deeply or superficially located because different homing mechanisms have been identified with regard to this anatomical distinction in rodents.<sup>47,48</sup> In humans, deep cervical LNs are obtained by the classical Daniel's biopsy.

## CONCLUSIONS

Several other potential MALT structures have been named in the literature, but they are not as well characterized as those mentioned in **Table 2**. Some examples are 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).

It is strongly recommended that immunologists standardize their terminology. To draw a correct functional map of immune compartments, it requires knowledge of the actual “landscape” in terms of anatomy/histology. It is important to know the definition of a lymphoid tissue, which for mucosal compartments appropriately applies only to the organized MALT structures. The mucosal effector sites, represented by LP and surface epithelium, exert distinct functions and cannot, by established classical definition, be called lymphoid tissues; they should hence not be referred to as belonging to MALT. Also notably, different cues are operating in mucosal inductive vs. mucosal effector compartments, with regard to both organogenesis and homing mechanisms. Such knowledge is mainly derived from genetically manipulated mice, and scientists should be aware of the fact that fundamental species differences exist within the mucosal immune system.

Finally, this system should not be called the “common” mucosal immune system, which may be taken erroneously to suggest uniform integration of all mucosal effector sites. We now know that the homing of primed immune cells to the various mucosal tissues is only partially integrated because the local extravasation, migration, and retention cues are largely site-specific.<sup>7,9,38,44</sup> The nomenclature described above for the mucosal immune system is in harmony with its compartment-

alized functional specialization as well as the classical concepts of histology.

## DISCLOSURE

The author declared no conflict of interest.

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