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*Short Communications*

# Expression of MAdCAM-1 and PNAd in Inflammatory and MALT Lymphoma Tissues of Ocular Adnexa, Thyroid, Salivary Gland and Lung

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Mucosa-associated lymphoid tissue (MALT) lymphomas usually arise from acquired MALT induced by chronic inflammation or autoimmune processes. In MALT of the gastrointestinal tract lymphocyte homing mechanisms operate primarily through interactions between integrin, expressed on mucosal lymphocytes, and MAdCAM-1, expressed on endothelium of high endothelial venules (HEV). In the present study, the expression of MAdCAM-1 and peripheral lymph node vascular addressin (PNAd) was examined immunohistochemically in normal, inflamed and MALT lymphoma tissues of various organs. It was shown that MAdCAM-1 was expressed on HEV in the gastrointestinal tract and thyroid that are inflamed or affected with MALT lymphomas, but not in the ocular adnexa, lung, and salivary gland. In contrast, PNAd was consistently expressed in all of the inflammatory or lymphomatous lesions examined, but not in the normal tissues. Expression of MAdCAM-1 on HEV may play an important role in lymphocyte migration at sites of chronic inflammation or MALT lymphoma of the gastrointestinal tract and thyroid. In other organs, PNAd may have the greater role.
**Key words** MAdCAM-1, PNAd, chronic inflammation, MALT Lymphoma

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) is a distinct type of low-grade B-cell lymphoma with unique histopathological and clinical features[1,2]. MALT lymphomas arise from acquired MALT which develops at sites of chronic inflammation in response to either infection, such as *Helicobacter pylori* gastritis, or autoimmune conditions, such as Hashimoto's thyroiditis or Sjögren's syndrome[2-5]. MALT lymphomas tend to remain localized to their site of origin for extremely long periods without distant dissemination[6]. Lymphocyte homing mechanisms may be at least partly related to this biological behavior.

Most mature lymphocytes migrate continuously form blood to tissue then back to blood. The lymphocyte homing is largely determined by various homing receptors and their vascular ligands. Homing of circulating lymphocytes from blood to both normal and inflammatory tissues is partly regulated by highly specific interactions between the cell surface homing receptors of lymphocytes and their endothelial ligands expressed on high endothelial venules (HEV) of the peripheral lymph nodes, MALT, and sites of chronic inflammation[7-9]. Lymphocyte homing to Peyer's patches and mesenteric lymph nodes is mediated through interactions between $\alpha_4\beta_7$ integrin expressed on mucosal lymphocytes and mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1)[10,11]. In the previous study, we examined expression of $\alpha_4\beta_7$ integrin and MAdCAM-1 in MALT lymphomas and revealed that neoplastic cells in the gastrointestinal low-grade MALT lymphomas consistently express $\alpha_4\beta_7$ integrin and tend to lose its expression after high-grade progression[12]. Preliminary study on MAdCAM-1 expression also revealed consistent expression on HEV in the gastric mucosa of chronic gastritis

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and MALT lymphoma[12]. In mice and rats it has been reported that MAdCAM-1 is expressed on HEV in normal and chronically inflamed pancreas and in intestinal mucosa and submucosa, but not in the normal thymus, esophagus, salivary gland, lung, liver, bladder, skin, or inflamed lacrimal gland[13–15]. Recent studies in humans have revealed that MAdCAM-1 is expressed in the intestinal tract, but there is little data regarding expression in other organs. In this study, we examined expression of peripheral lymph node vascular addressin (PNAd) known to mediate lymphocyte migration to the peripheral lymph node and to sites of inflammation[9]. We also examined the expression of MAdCAM-1 in the human ocular adnexa, salivary gland, thyroid gland and lung in the normal, inflammatory or lymphomatous state by the immunohistochemical method.

Deparaffinized tissue sections were obtained from 58 cases of low-grade MALT lymphoma (18 stomach, 12 ocular adnexa, 14 thyroid, 7 salivary gland and 7 lung) and 24 cases of chronic inflammation (9 thyroid and 15 salivary gland). The sections were immunostained by the indirect immunoperoxidase method using dextran polymer-conjugated secondary antibody labeled with peroxidase (EnVision+, DAKO Japan, Kyoto) as described previously[12]. Anti human MAdCAM-1 (10A6) and PNAd (MECA79) were used as the primary monoclonal antibodies.

Immunohistochemical staining showed that MAdCAM-1 was expressed consistently on HEV in the gastric mucosa of lymphomatous lesions of gastric MALT lymphoma and chronic gastritis. In the thyroid, MAdCAM-1 was selectively expressed on endothelial cells of HEV in the lymphomatous lesions of half the cases of thyroidal MALT lymphoma and in the inflamed tissues of two-thirds of the cases of chronic

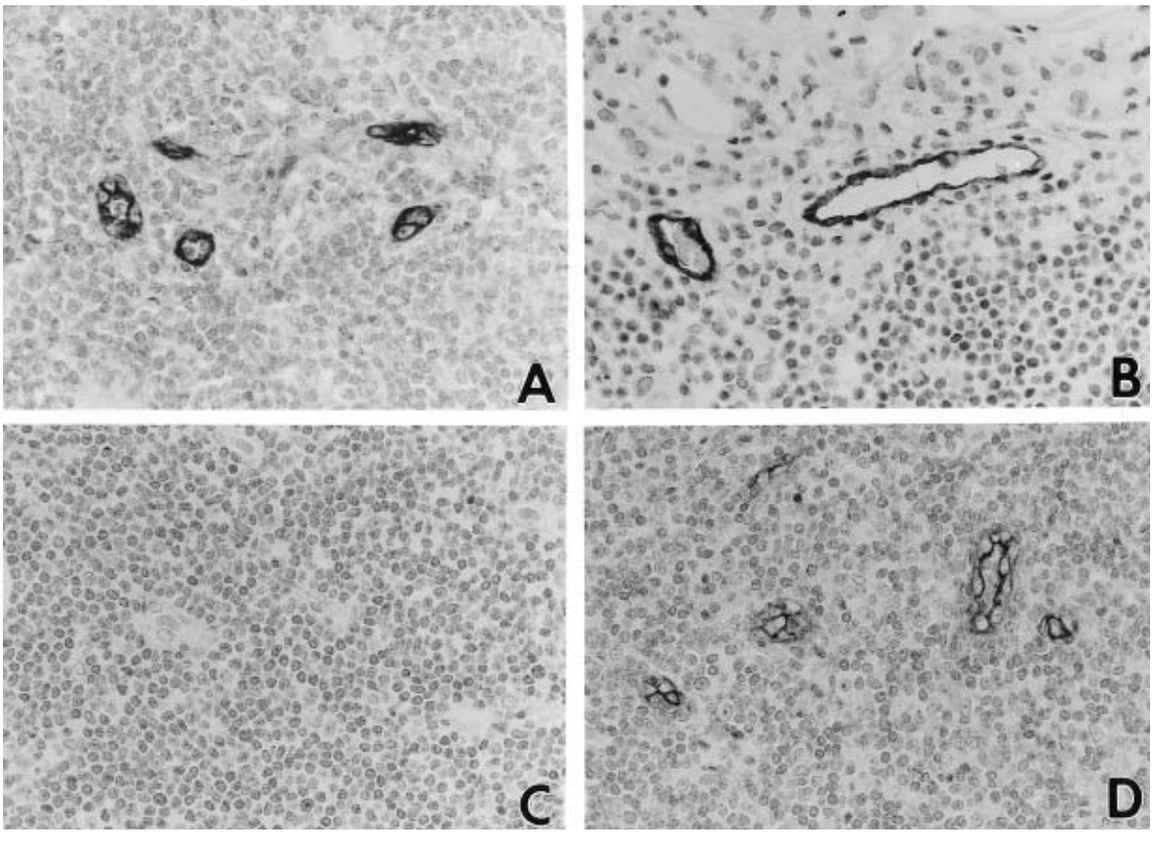


**Fig. 1.** Immunohistochemical staining for MAdCAM-1 and PNAd.
(A) MALT lymphoma of the thyroid. MAdCAM-1. ×280.
(B) Hashimoto's thyroiditis. MAdCAM-1. ×290.
(C) MALT lymphoma of the salivary gland. MAdCAM-1. ×250.
(D) MALT lymphoma of the salivary gland. PNAd. ×250

**Table 1** Expression of MAdCAM-1 and PNAd in stomach, ocular adnexa, thyroid, salivary gland and lung

| Organ | Disease | MAdCAM-1 | PNAd |
|---|---|---|---|
| Stomach | Low-grade MALT lymphoma | 18/18* | 18/18 |
| | Chronic gastritis | 19/19 | 14/19 |
| Ocular adnexa | Low-grade MALT lymphoma | 0/12 | 12/12 |
| | Reactive lymphoid hyperplasia | 0/5 | 5/5 |
| | Normal mucosa | 0/5 | 0/5 |
| Thyroid | Low-grade MALT lymphoma | 7/14 | 14/14 |
| | Chronic thyroiditis | 6/9 | 9/9 |
| | Normal mucosa | 0/9 | 0/9 |
| Salivary gland | Low-grade MALT lymphoma | 0/7 | 7/7 |
| | Chronic sialadenitis | 0/15 | 13/15 |
| | Normal mucosa | 0/15 | 0/15 |
| Lung | Low-grade MALT lymphoma | 0/7 | 6/7 |
| | Nonspecific interstitial pneumonia | 0/5 | 2/4 |
| | Reactive lymphoid hyperplasia | 0/1 | 1/1 |
| | Normal pulmonary tissue | 0/5 | 0/5 |

*, This data has been reported in reference 12.

thyroiditis, including Hashimoto's thyroiditis (Fig. 1, A, B ; Table 1). Normal thyroid tissues lacked MAdCAM-1 expression. Although their rates of positive expression were lower than that in gastrointestinal, low-grade MALT lymphomas. The lymphocyte homing mechanism, through interaction of $\alpha_4\beta_7$ integrin and MAdCAM-1, could be related to the biological behavior of MALT lymphoma in the thyroid, as is the case with gastrointestinal expression. In contrast, the venular endothelium of the ocular adnexa, lung, and salivary gland never expressed MAdCAM-1, even at the site of normal tissues and inflamed or lymphomatous lesions (Fig. 1, C). On the other hand, PNAd was expressed consistently in all the inflammatory or lymphomatous lesions that we examined (Fig. 1, D) but not in normal tissues of the ocular adnexa, thyroid gland, salivary gland and lung. This means that PNAd may play a role in lymphocyte homing to the inflamed lesions and in biological behavior of lymphoma cells in MALT lymphoma tissues of these organs.

MAdCAM-1 is important in regulating lymphocyte-trafficking to (gastrointestinal) mucosal sites. And MALT lymphoma cells are thought to originate from acquired chronically inflammatory lesions. Interestingly, MALT lymphomas often form multiple lesions in a single organ, such as the stomach and colorectum. We suppose that this multiplicity is closely related to the expression of adhesion molecules, because neighboring lymph nodes are not usually involved through lymphoma cells. Moreover, we previously reported on the clinicopathological character of multi-organ MALT lymphomas and described frequent MALT lymphoma migration (metastases) to MALT organs without lymph node involvement[16]. This also suggests that MALT lymphoma movement depends on organ-specific adhesion systems.

While the homing receptors $\alpha_4\beta_7$ integrin/MAdCAM-1 for the gastrointestinal tract and L-selectin/PNAd for the peripheral lymph nodes have been identified, details are sparse regarding which adhesion receptors are actually used by lymphocytes of MALT organs and peripheral lymph nodes. The $\alpha_4\beta_7$ integrin is widely expressed by leukocyte subsets in the blood, organized lymphoid tissue, intestinal lamina propria[17–22] but do not play a major role in homing of lymphocytes in the lacrimal glands, thyroid, and lung in inflammation or MALT lymphoma[12,14,23–25]. L-selectin regulates lymphomyte homing to the peripheral lymph node and lacrimal glands[9,14], but occasionally positive in normal salivary gland, primary Sjögren's syndrome and thyroid MALT lymphoma[12,26]. In the lung, expression of L-selectin varies according to the stimuli used for initiating inflammation[23–25,27,28].

In conclusion, it has been shown that human MAdCAM-1 preferentially acts as a vascular addressin for lymphocytes, not only in the gastro-

intestinal tract, but also in the thyroid gland, and that the lymphocyte homing mechanism may affect the biological behavior of MALT lymphoma cells in these organs through an interaction between MAdCAM-1 and $\alpha_4\beta_7$ integrin. PNAd is expressed more ubiquitously on venular endothelium at the site of inflammation and may be partly related to the biology of MALT lymphoma arising from the organs other than the gastrointestinal tract and thyroid.

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