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Review article

Expression of potential lymphocyte trafficking mediator molecules in the mammary gland

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Abstract – The mammary gland performs a variety of immunological functions, including protecting itself from mastitis and protecting neonates from infectious agents. Several molecules that mediate lymphocyte trafficking in the immune system are also expressed in the mammary gland. This review is focused on the immunological function of these molecules, especially glycosylation-dependent cell adhesion molecule-1 (GlyCAM-1) and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) in the mammary gland. GlyCAM-1 is expressed in the lactating mouse mammary gland. Endothelial cells produce this protein and secrete it into milk. The glycosylated modification of mammary gland GlyCAM-1 is different from that of the lymph nodes, and lacks the binding ability for L-selectin on lymphocytes. GlyCAM-1 in the mammary gland is not involved in lymphocyte migration, and probably has another function besides that of the lymph nodes. MAdCAM-1 is expressed on endothelial cells of small venules around mouse mammary lobules during lactation. This molecule has the ability to interact with $\alpha_4ß_7$ integrin on lymphocytes and mediates lymphocyte recruitment to the mammary gland. The density of $ß_7^+/CD3^+$ T-cells is correlated with the density of the MAdCAM-1-stained area, suggesting that MAdCAM-1 may mediate the migration of these cells. In contrast, there is no relationship between MAdCAM-1 expression and the number of $ß_7^+$/c-IgA^+ B-cells, implying that some other factor is involved in lymphocyte migration to the mammary gland. Chemokines, such as IL-8, GRO-α, MCP-1, RANTES and MEC, have been detected in human and mouse mammary glands. Although little information is available, these molecules may contribute to lymphocyte migration to the mammary gland.

mammary gland / mucosal-associated lymphoid tissue (MALT) / glycosylation-dependent cell adhesion molecule-1 (GlyCAM-1) / mucosal addressin cell adhesion molecule-1 (MAdCAM-1) / lymphocyte migration

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1. INTRODUCTION

The mammary gland is one of the mucosal tissues [16]. It is one of the sites where bacteria attack frequently. Mastitis, infection of the mammary gland, causes much economic loss in the milk industry [17]. To defend itself against mastitis, the mammary gland has a variety of defense mechanisms, similar to other mucosal-associated lymphoid tissues [16, 40, 42]. The mammary gland also has another immune function, such as protecting pups or infants from infection by giving immunoglobulins, lymphocytes and immune reagents with milk [21, 33, 37, 42]. Immunoglobulins in milk are important for the development of the neonatal immune function [27, 28]. Many lymphocytes are also found in the milk and these cells may also protect newborn infants from infection [8, 9].

Many investigators have observed lymphocyte migration to the mammary gland [2, 12, 15, 24, 31, 51], and have thought that these lymphocytes mediate immune function. But, the migration mechanism has remained unknown. Recently in the immunological field, some molecules which mediate lymphocyte migration were found. Adhesion molecules [14, 29] belong to one of these families that mediate lymphocyte trafficking, and chemokines [3, 41] are the others. Nishimura et al. [34–36] and other investigators [42, 49] found that some of these molecules are expressed in the mammary gland. This review is focused on these molecules, especially glycosylation-dependent cell adhesion molecule-1 (GlyCAM-1) and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) in the mammary gland. I will discuss the functions of these molecules as determined from molecular studies.

2. LYMPHOCYTE CIRCULATION AND CELL ADHESION MOLECULES IN THE IMMUNE SYSTEM

Most mature lymphocytes circulate systematically in the body in order to regulate the immune function appropriately [22, 32]. This phenomenon suggests that there are some interactive mechanisms between lymphocytes and endothelial cell mediated tissue specific migrations. Stamper and Woodruff [46] established an in vitro model system to study the interaction between lymphocytes and high-endothelial venules (HEV), which is the place where lymphocytes enter into the lymph nodes [20].

This assay system was used to make monoclonal antibodies (mAbs) against surface molecules of lymphocytes or endothelial cells which blocked the binding for tissue specific HEV. One of these mAbs, which recognized a surface molecule of the lymphocyte, blocked lymphocyte adhesion to peripheral lymph node HEV, but not to Peyer's patches [19]. This molecule was characterized and was named L-selectin [25, 29]. This L-selectin is expressed on naïve T and B cells, and it is important for the tissue specific migration of these cells. The in vitro assay using frozen sections as well as in vivo studies have shown the importance of this molecule. The in vivo administration of mAb to L-selectin or the preincubation of lymphocytes with L-selectin mAb completely blocks the migration of lymphocytes to lymph nodes [19]. L-selectin knockout mice have small, hypocellular lymph nodes [1].

Since L-selectin in lymphocytes is important for migration, many investigators have searched for ligands of this molecule. Glycosylation-dependent cell adhesion molecule-1 (GlyCAM-1) was initially cloned as an L-selectin ligand, expressed in the HEV of lymph nodes [30] (Fig. 1). GlyCAM-1 is a novel mucin-like molecule containing two regions of clustered serine/threonine residues, with a molecular weight of 50 kDa. The presentation of carbohydrates in a mucin-like structure is necessary for the affinity interaction with L-selectin. Although this molecule was detected in association with adhesion molecules, it is a secretory protein with no

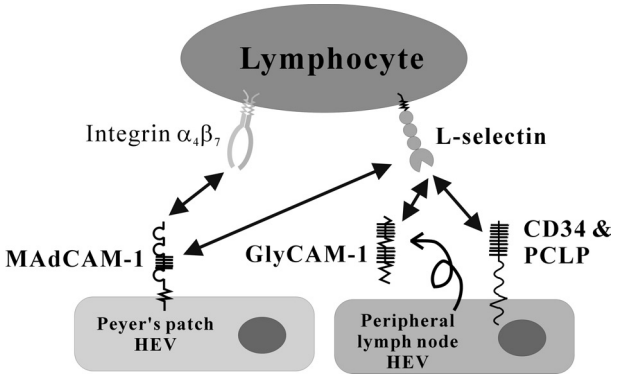

Figure 1. Function of GlyCAM-1 and MAdCAM-1 in lymph nodes or Peyer's patches. Glycosylation-dependent cell adhesion molecule-1 (GlyCAM-1) is expressed in the lymph node high endothelial venule (HEV) and is secreted protein. This GlyCAM-1 interacts with lymphocyte L-selectin which is important for lymphocyte migration to the lymph nodes. Another molecules, such as sialomucin CD34 and podocalyxin-like protein (PCLP), also interact with L-selectin. Mucosal addressin cell adhesion molecule-1 (MAdCAM-1) is expressed on the Peyer's patch and mesenteric lymph nodes HEV. This MAdCAM-1 interacts with lymphocyte integrin $\alpha_4\beta_7$ and mediates the lymphocyte attaching to HEV. MAdCAM-1 in mesenteric lymph nodes or Peyer's patches has a specific glycosylated modification and has the ability to bind with L-selectin.

transmembrane site [30]. Analysis of the GlyCAM-1 knockout mouse has shown implication of other molecules in lymphocyte recruitment to HEV [25]. The GlyCAM-1 knockout mouse exhibited normal lymphoid organ architecture and normal lymphocyte homing to lymph nodes. Several other molecules, Sgp90 and Sgp200, have mentioned as ligands for L-selectin [23] and these molecules may contribute to lymphocyte trafficking to HEV with GlyCAM-1 (Fig. 1). Sgp90 was characterized as sialomucin CD34 and podocalyxin-like protein (PCLP) [5, 43], however Sgp200 is not yet characterized. L-selectin recognizes a specific sulfated form of these molecules and basic structure was reported [13, 26].

Another group made mAbs against surface molecules of endothelial cells by using Stamper Woodruff assay. One of mAbs, MECA-367, blocked the binding of lymphocytes to HEV of mesenteric lymph nodes or Peyer's patches, but not of peripheral lymph nodes [47]. The molecule, which was recognized by this mAb, was characterized and named mucosal addressin cell adhesion molecule-1 (MAdCAM-1) [10] (Fig. 1). MAdCAM-1 contains immunoglobulin-like domains and one serine/threonine-rich domain, exhibiting a sequence characteristic of mucin. The search for the MAdCAM-1 receptor has revealed that MAdCAM-1 is the ligand for $\alpha_4\beta_7$ integrin on lymphocytes [7]. The structural analysis of the binding site has revealed that the first immunoglobulin-like motif is important for the interaction with $\alpha_4\beta_7$ integrin [11, 50]. A subset of MAdCAM-1 isolated from mesenteric lymph nodes or Peyer's patches can also interact with L-selectin, whereas MAdCAM-1 isolated from tumor necrosis factor (TNF)-α-stimulated cultured endothelioma cells cannot [6]. This indicates that a particular variant of MAdCAM-1 on HEV expresses a specific carbohydrate structure that supports the interaction with L-selectin [6].

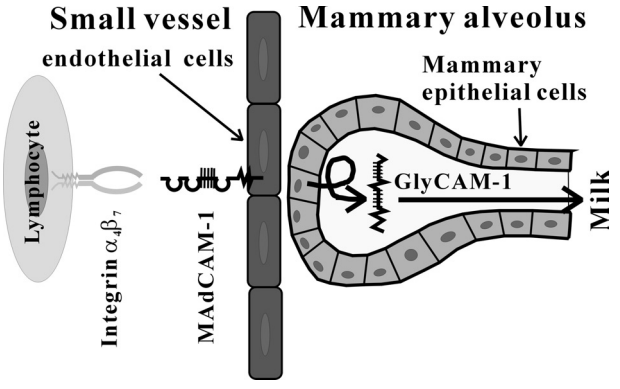

Figure 2. Function of GlyCAM-1 and MAdCAM-1 in the lactating mouse mammary gland. Glycosylation-dependent cell adhesion molecule-1 (GlyCAM-1) is produced by mammary epithelial cells and secreted into milk. This GlyCAM-1 has a different glycosylated form than that of the lymph nodes, and does not have the ability to interact with L-selectin. Mucosal addressin cell adhesion molecule-1 (MAdCAM-1) is expressed on the endothelial cells of small vessels around the mammary lobules. This MAdCAM-1 interacts with integrin $\alpha_4ß_7$ on lymphocytes and mediates lymphocytes migration to the mammary gland.

3. GlyCAM-1 AND MAdCAM-1 IN THE MAMMARY GLAND

GlyCAM-1 is expressed in the lactating mouse mammary gland [18, 34]. Its expression is difficult to detect in the virginal stage but is induced from late pregnancy and continues into lactation. GlyCAM-1 is expressed by mammary epithelial cells, which secrete it into milk (Fig. 2). Its molecular weight in the mammary gland is about 26 kDa vs. 50 kDa in lymph nodes [36], suggesting that the glycosylation structure, which is important for the interaction with L-selectin, differs from that of lymph node GlyCAM-1. Mammary GlyCAM-1 does not bind to L-selectin-immunoglobulin chimeric protein and lacks the ability to interact with L-selectin on lymphocytes [18]. These data indicate that mammary GlyCAM-1 is not involved in lymphocyte trafficking and may have another function in milk (Fig. 2).

MAdCAM-1 is also expressed in the mouse mammary gland, and histochemical analysis has indicated that the expression is located on endothelial cells of the venule surrounding the mammary lobules [35, 48] (Fig. 2). Reverse transcription-polymerase chain reaction (RT-PCR) analysis [35] revealed that the expression of MAdCAM-1 in the mouse mammary gland is stage specific. Slight expression has been detected in the virgin mammary gland, increasing during pregnancy, and reaching a peak in the early lactating mouse mammary gland. Histochemical analyses using anti-MAdCAM-1 monoclonal antibody, and measurement of the MAdCAM-1 staining area, have yielded the same expression kinetics during pregnancy [48]. Following parturition, the staining area decreases throughout lactation. Interestingly, the kinetics of $ß_7^+/CD3^+$ lymphocyte cell numbers in the mammary gland exhibit the same pattern as MAdCAM-1 staining, with an increase during pregnancy and decrease after parturition. These results suggest that the mammary gland expression of MAdCAM-1 mediates $ß_7^+/CD3^+$ T-cell migration.

Although the ligand for MAdCAM-1 in the mammary gland has not been directly demonstrated, the following evidence supports MAdCAM-1 interaction with $\alpha_4ß_7$ integrin on lymphocytes. Mouse mammary gland MAdCAM-1 can be recognized by the monoclonal antibody MECA-367 [35, 48]. This antibody blocks lymphocyte binding to MAdCAM-1 [47] and probably recognizes the binding site of MAdCAM-1 to integrin. RT-PCR analysis has also demonstrated that mammary MAdCAM-1 contains the binding site [35]. The PCR product includes the first immunoglobulin-like motifs that are important for the interaction with $\alpha_4ß_7$ integrin [11, 50]. Although mammary MAdCAM-1 apparently interacts with α4ß7 integrin, it does not interact with L-selectin, another ligand for HEV MAdCAM-1. HEV MAdCAM-1 is recognized by the L-selectin immunoglobulin chimeric protein, but mammary MAdCAM-1 is not (T. Nishimura, unpublished data). This finding indicates that mammary MAdCAM-1 has a different carbohydrate structure than HEV MAdCAM-1 and lacks the ability to interact with L-selectin (Fig. 2).

4. OTHER POTENTIAL LYMPHOCYTE TRAFFICKING MEDIATOR MOLECULES IN THE MAMMARY GLAND

Mechanisms for lymphocyte migration are required for the proper immune functioning of the mammary gland. MAdCAM-1 is apparently one molecule involved in mediating lymphocyte trafficking to the mammary gland. MAdCAM-1 is expressed on small vessels around the alveoli and mediates $ß_7^+/CD3^+$ T-cell recruitment during lactation [35, 48]. The extent of MAdCAM-1 staining and the number of $ß_7^+/CD3^+$ T-cells in the mammary gland change similarly during pregnancy and lactation, strongly suggesting that MAdCAM-1 mediates lymphocyte migration [48].

Although MAdCAM-1 is one candidate for the mediation of lymphocyte migration to the mammary gland, other factors are obviously involved. All lymphocytes migration to the mammary gland cannot be completely explained by MAdCAM-1 expression. For example, the numbers of $ß_7^+$/c-IgA^+ B-cells do not correlate with MAdCAM-1 expression [48]. The MAdCAM-1 staining area increases during pregnancy and then decreases during lactation; however there is no change in the number of $ß_7^+$/c-IgA^+ cells during pregnancy, and they increase during lactation. Another investigation [49] has also showed that IgA-producing plasma cell numbers and MAdCAM-1 expression are not related. These results invoke the involvement of other factors in the mediation of lymphocyte migration in the lactating mammary gland. The cell adhesion molecule GlyCAM-1 is also expressed in the mammary gland, although these molecules do not have a role in mediating mammary lymphocyte migration [18, 34]. GlyCAM-1 is expressed by mammary epithelial cells and secreted into milk without the ability for interaction with L-selectin on lymphocytes [18]. GlyCAM-1 in the mammary gland should therefore have another function than the mediator of lymphocyte migration.

Some other molecules which mediate lymphocyte migration have been reported to be expressed in the mammary gland. VCAM-1 has been detected in the lactating mouse mammary gland [48]. But, the expression has been only detected on some large blood vessels and has never been detected on small vessels, which is the site from which the lymphocytes extravasate. IL-8, a chemokine, is present in human [38] and bovine milk. The concentration of bovine IL-8 is upregulated during mammary gland infections [4, 44]. The large increase in IL-8 concentration suggests that this chemokine may be involved in leukocyte recruitment to the site of infection, even though there is little information on IL-8 being involved in lymphocyte

migration under normal conditions. Chemokines, GRO-α, MCP-1 and RANTES have also been detected in human milk [45], and Mucosae-associated epithelial chemokine (MEC) is detected in the mouse mammary epithelial cells [39]. Although, to date, only limited information is available, the current data suggest that some of these molecules may contribute to lymphocyte migration to the mammary gland.

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