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LYVE 1 AND VE-CADHERIN AS A MARKER FOR LYMPHATIC AND VASCULAR ENDOTHELIAL CELLS

[1]Dr. T. Jahira Banu, [2*]Dr. Yogesh Ashok Sontakke and [3]Dr. Dharmaraj W. Tamgire

[1]Junior Resident, Department of Anatomy, JIPMER.
[2]Associate Professor, Department of Anatomy, JIPMER.
[3]Associate Professor, Department of Anatomy, JIPMER.

***Corresponding Author: Dr. Yogesh Ashok Sontakke**
Associate Professor, Department of Anatomy, JIPMER.

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ABSTRACT
Cell surface proteins expressed on the surface of cells that often serve as a marker for specific cell types. The proteins in the endothelium of blood vessels and lymphatic vessels were targeted for many diagnostics procedure. It acts as a tool for defining the normal endothelial monolayer and its variations in pathological state. Two such proteins are reviewed in this article, one is the VE-Cadherin protein located in the endothelial cell junction and the other one is LYVE 1 protein present over the surface of lymphatic endothelium.

KEYWORDS: VE-Cadherin, LYVE-1, Marker.

INTRODUCTION
The endothelium plays an important role in the maintenance of tissue integrity and homeostasis by controlling the normal flow of blood and lymph in the body's circulatory system. The endothelial monolayer is formed by the adherence of endothelial cells with the help of junctional complexes. The proteins of the endothelium serve many important roles for maintaining monolayer integrity and helpful in preventing the derangements of physiological functions. Derangements of its microstructural properties of the endothelium can also be studied with the help of these proteins. Therefore, the protein surrounding the endothelial cells serve as a marker for defining the endothelium and its associated disease. Studies have been conducted by coding the endothelial cell protein as a marker.

Two such proteins called VE-Cadherin and LYVE-1 are used in several studies for the identification of endothelium of blood vessels and lymphatic vessels. VE-Cadherin is a vascular endothelial binding protein located in the transmembrane junction between the endothelial cells. It maintains a balance between the intercellular junction plasticity and integrity, through its adhesive and signaling properties. It helps in preventing the formation of platelet deposition and thrombus formation.[1] LYVE 1 is a lymphatic vessel endothelial hyaluronan receptor 1 found on the surface of lymphatic endothelial cells. It acts as a receptor protein for binding the hyaluronan, a primary component of the extracellular matrix.[2] Disruption of endothelial monolayer is a hallmark for many pathological and disease states such as atherosclerosis, diabetes, hypertension, inflammation, and tumor metastasis.[3]

The importance of VE-cadherin and LYVE 1 is that it can be used in all branches of endothelial cell biology. These proteins can be used for identifying the endothelium, there by the nature of normal vascular and lymphatic system and in disease conditions can be very well understood.[4] This review will focus on VE-cadherin and LYVE-1 proteins utility and its usage as a marker.

MATERIALS AND METHODS
Articles were collected from the PubMed and google scholar for writing review on LYVE1 and VE-Cadherin. The VE-cadherin, LYVE1, and immunohistochemistry were used as a search word. Articles involving human studies and English language were included and the articles involving animals and other languages were excluded.

REVIEW
VE-Cadherin
VE-Cadherin is the type of calcium-dependent cell adhesion molecule seen in vascular endothelial cells. The cell to cell adhesion of endothelial cells is mediated by the adherens junction complex with the help of cadherin domains. It is encoded by the human gene Cadherin 5 (CDH5).[5] The integrity of the blood vessel is maintained by this transmembrane adhesion molecule. VE-Cadherin has both adhesive and signaling properties. Through these properties, it maintains a balance between intercellular junction plasticity and integrity, a

requirement for endothelial cells to maintain the proper barrier function of blood vessels. VE-cadherin connected via its cytoplasmic tail to actin filaments by a complex of proteins including α- and β-catenins, plakoglobin (γ-catenin), p120-catenin, vinculin and α-actinin that are useful for opening and closing of junctions as well as for maintaining the stability of the junctions.[5,6]

Moreover, experimental evidence indicates that reduced expression of cadherins in tumor cells may have a pathogenetic role in facilitating cell detachment and invasiveness. Angiogenesis, the sprouting of new vessels from the existing vasculature can be identified. It is a tightly controlled process that plays its most obvious role in early development of tumour cells. The tendency of VE-cadherin to disappear in malignant vascular tumours hampers its utility as a histogenetic marker for tumour diagnosis.[7] Figure 1 depicts the diagrammatic representation of VE-Cadherin molecule.

Synonyms of VE-Cadherin: 7B4 Antigen, Cadherin-5, Vascular endothelial cadherin.

LYVE 1

The lymphatic system acts as a drainage system for the extracellular fluid, drains extracellular fluid from the tissues and provides an exclusive environment in which immune cells can respond to the foreign antigen. The knowledge of the molecular biology of the lymphatics are scanty, owing to longstanding difficulties in demarcating the lymphatic endothelial cells. Receptors are discovered and used as a marker for isolating the lymphatic endothelial cells. One such receptors are called LYVE 1 receptor. LYVE1 is a type I integral membrane glycoprotein present on lymphatic endothelial cells. It acts as a cell surface receptor for binding the soluble and immobilized hyaluronan. It is encoded by the LYVE1 gene. Hyaluronan (HA), a large mucopolysaccharide copolymer of N-acetyl D-glucosamine and D-glucuronic acid, abundant in the extracellular matrix of tissues throughout the body.[2] It is an glycosaminoglycan produced by the plasma membrane distributed throughout the connective, epithelial, and neural tissues. It facilitates cell migration during inflammation, wound healing, metastasis, and embryonic morphogenesis.[9] Lymphatic vessel endothelial hyaluronan receptor-1 has a 41% similarity to CD44, and LYVE-1 expression is largely restricted to endothelial cells of lymphatic vessels and splenic sinusoidal endothelial cells.

Banerji et al. discovered this receptor LYVE 1 after a series of procedures. They described that the LYVE 1 receptor present preferentially, if not exclusively on lymphatic endothelium.[2] Jackson G D et al described that the LYVE 1 has binding site called the Link module.

Banerji et al. commented that Lymphatic vessels are morphologically distinguishable from blood vessels by their reduced or missing basement membrane and lack of erythrocyte content. LYVE-1 by contrast appears to be restricted to relatively non-motile lymphatic endothelial cells, where it seems more likely to function in the immobilization of Hyaluronic acid in the vessel lumen, rather than in its recognition as a positional cue for migration. Mumprecht et al. used 124I-labeled antibody against LYVE-1 (124I-anti-LYVE-1) for *in vivo* imaging of inflammation- and tumor-induced LN lymphangiogenesis with positron emission tomography (PET).[10] Expression of LYVE 1 was undetectable on lymphocytes, hematopoietic cells, or vascular endothelial cells. Apart from lymphatic endothelium, LYVE-1 is expressed in normal liver blood sinusoids, spleen endothelium and activated tissue macrophages.[11] Importantly however, LYVE-1 has not been detected in blood vascular endothelium, with the only known exception being a proportion of blood vessels in the lung—a cell type that is specialized for gaseous exchange.[8] Figure 2 depicts the diagrammatic representation of LYVE-1 molecule.

Synonyms: Lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1), also known as extracellular link domain containing 1 (XLKD1) is a Link domain-containing hyaladherin, a protein capable of binding to hyaluronic acid (HA), Cell surface retention sequence-binding protein 1- CRSBP-1, HAR- hyaluronic acid receptor, lymphatic vessel endothelial hyaluronan receptor 1.

Images

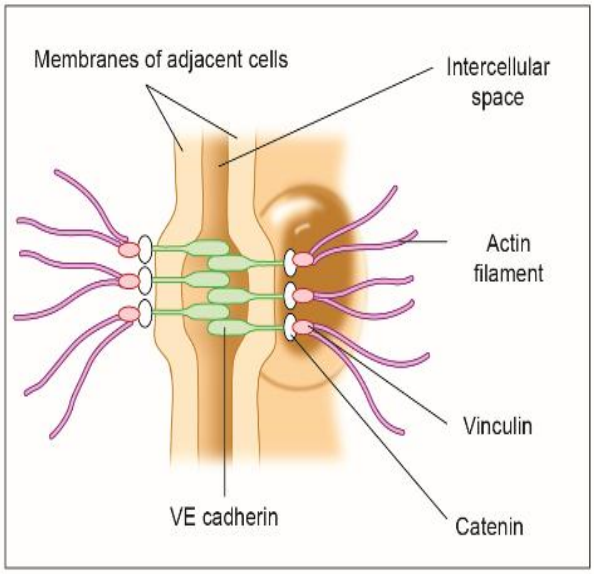

Figure 1: VE – Cadherin molecule.

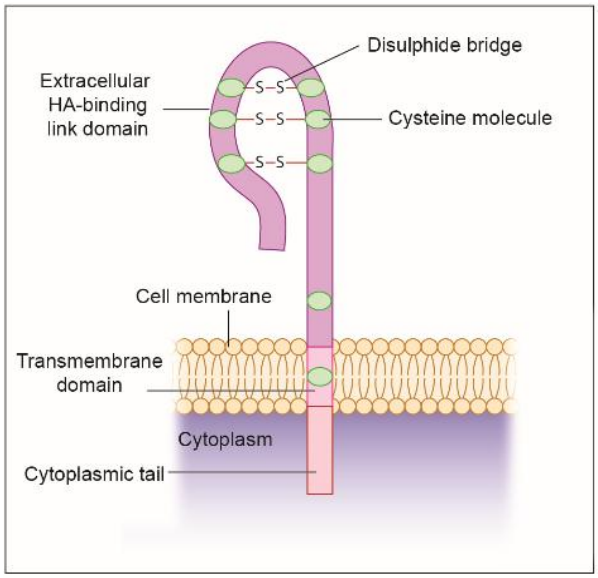

Figure 2: LYVE-1 molecule.

CONCLUSION

LYVE-1 is a cell surface receptor used as a lymphatic endothelial cell marker, allowing for the isolation of these cells for experimental purposes. This protein may function in lymphatic hyaluronan transport and have a role in tumor metastasis. Hence, LYVE1 is the first lymph-specific HA receptor to be characterized and is a uniquely powerful marker for lymph vessels themselves. Deciphering the importance of VE-cadherin, and understanding how they contribute for targeting the endothelium of vascular channels, is an important area for future research. These studies may lead to the discovery of new therapeutic targets for the many inherited and pathological diseases associated with endothelial dysfunction.

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