Review Article

Histomolecular Structural Aspects of High Endothelial Vessels in Lymph Node and Its Significance in Oral Cancer and Metastasis

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Abstract

Molecular cancer research studies focus on identifying diagnostic, screening, and metastatic indicators, and monitoring therapeutic responses. Migration of tumor cells and lymphocytes are important aspects in metastasis. High endothelial vessels are specialized histological structures identified in the blood vessels in lymphoid organs, which allow the migration of lymphocytes. In the recent decades, the role of high endothelial vessels is being addressed in cancer metastatic research. This review article is to highlight the histological and molecular structural aspects of high endothelial venules (HEVs) in the lymph node, and to demonstrate the role of HEVs in oral cancer metastasis, specifically oral and pharyngeal squamous cell carcinoma. The literature for the present paper were searched from the data sources such as Medline/PubMed, CINAHL plus, and gray literature sources from inception to May 2015. Searches were conducted using both free texts and medical subject headings related to the title of the present paper. Only the full text manuscripts of the search results that support the objective(s) of the paper and papers written in English were included. HEVs are unique structures that are identified in the lymphocytes and primarily assist in the lymphocytic migration from the blood stream into the lymph node. Understanding the histomolecular characteristics of HEV will allow researchers to develop novel therapeutic approaches in cancer tissues.

Keywords: High endothelial vessels, lymph node (LN), metastasis, oral cancer, oropharyngeal squamous cell carcinoma, tumor immunotherapy

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Introduction

Cancer research has taken a paradigm shift toward metastasis as the molecules involved in the metastatic process are known to have a substantial role in prognosis and therapeutic response. Oropharyngeal squamous cell carcinoma (OPSCC) is the eighth most common cancer among men in the world, the most common sites being the pharynx and tongue.[1] The 5-year survival rate for oral cancer has remained at 50-55% for several decades and has not improved significantly despite advances in surgery and radiation therapy.[2,3] Mortality mainly results from metastatic disease and local recurrence. The metastasis of tumor cells to the draining lymph nodes is usually the initial step in the systemic spread of cancer. It is the most unfavorable prognostic factor

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influencing the survival outcome in many carcinomas including OPSCC.[4-7]

The first draining lymph node (LN) is the "sentinel node" and the term was coined by Cabanas three decades ago.[8] The primary tumor induces morphological and functional changes in the sentinel lymph node. The vasculature and the lymph channels undergo reorganization before the arrival of cancer cells. The key blood vessels that are remodeled in the lymph nodes are identified as high endothelial venules (HEVs).[9] HEVs are specialized blood vessels in the paracortical region of the lymph nodes that govern lymphocyte recruitment. The role of HEVs in human cancers have gained much attention because of the accumulating evidence suggesting that LN metastasis in human cancer may share similar mechanisms with lymphocyte trafficking.[10,11]

The present paper is aimed at highlighting the histological and molecular structural aspects of HEVs in the lymph node. In addition, it aims to demonstrate the role of HEVs in oral cancer metastasis, specifically oral and pharyngeal squamous cell carcinomas. To achieve our objectives, the present paper will be discussing the normal histomolecular characteristics of HEVs, lymphocyte migration and trafficking in HEVs, their role in metastatic process, and molecular studies of HEVs in benign and malignant oral cancers.

The literature was searched from the sources such as Medline/PubMed, CINAHL plus, and gray literature from inception to May 2015. The literature search was conducted using both free texts and medical subject headings related to the title of the present paper. The first and second authors of the current paper screened the titles and abstracts of the retrieved studies. The full texts of suitable papers that are related to the present paper's objective(s) were included. The articles that did not provide full text information, were not related to oral or pharyngeal squamous cell carcinomas, duplicating article titles, and non-English papers were excluded. Research papers for literature support were conducted independently by first and second authors. The selected papers were screened by first, second, and third authors and a decision was made for consideration. Selected papers were studied and were meaningfully summarized by all the authors for the synthesis of the current paper.

Architectural Quantum of Lymph Node and High Ebdothelial Venule

The LN is composed of numerous lymphoid lobules and lymph sinuses and is surrounded by a capsule. It is subdivided into the cortex superficially and medulla centrally. The lymphoid lobule is made up of superficial cortex and deep cortex (paracortex). The superficial cortex comprises a reticular meshwork with zones of communication for lymphocytes, macrophages, and antigen presenting cells. B lymphocytes accommodate themselves to the primary follicles in the superficial cortex where they interact with follicular dendritic cells. T lymphocytes reside in the deep cortical unit (DCU) of the paracortex where they interact with dendritic cells. The DCU has a center and a periphery. The peripheral DCU and the interfollicular cortex form the pathway for recruiting B lymphocytes and T lymphocytes via the cortical arterioles and HEVs[12] [Figure 1].

High Endothelial Venules

HEVs are specialized postcapillary venules seen in lymphoid tissues. The endothelial cells in HEV are plump and almost cuboidal in appearance, different from the flat morphology of cells that line the other vessels. They are called high endothelial cells with reference to their thickness. These endothelial cells express 6-sulfo sialyl Lewis(x) ligands for the lymphocyte homing receptor L-selectin, which mediates the initial capture and rolling of lymphocytes along the vessel wall.[13-15] Generally these HEVs are restricted to lymphoid organs but some evidences have shown blood vessels with HEV characteristics developing in nonlymphoid tissues in many chronic inflammatory diseases including rheumatoid arthritis, inflammatory bowel diseases, chronic gastritis, and autoimmune thyroiditis.[16-18]

Histomolecular Characteristics of High Endothelial Venules

Understanding the histological and cytological characteristics of HEV is significantly important prior

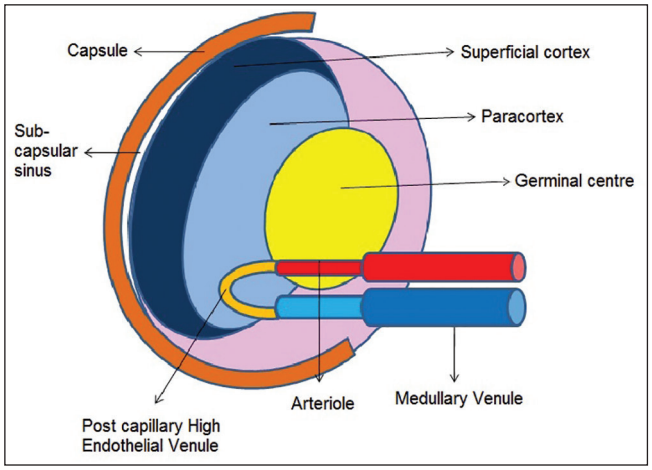

Figure 1: Cross-section of lymph node showing capsule, subcapsular sinus, superficial cortex, paracortex, germinal center, and lymphatic vessels such as arteriole, medullary venule, and postcapillary high endothelial venule

to the discussion of the molecular content of HEVs. Histologically HEVs are characterized by a single layer of endothelial cells [HEV endothelial cells (HEV-ECs)] contributing to form the inner endothelial layer, pericyte-like cells occupying the middle layer, and an outermost basal lamina[19] [Figure 2]. HEV-ECs are microscopically characterized by the tall, plump, cuboidal cells and are composed of free ribosomes, multivesicular bodies, well-developed golgi apparatus, tissue-specific adhesion molecules, and chemokines.[20] The interaction of tissue-specific adhesion molecules and chemokine molecules of high endothelial cells with circulating lymphocytes will facilitate selective permeability of lymphocytes from the circulating blood to LN and lymphoid nodules.[21] Pericyte-like cells are fibroblastic reticular cells (FRCs) and help in producing perivascular fibroreticular sheath (PFRS) [Figure 3]. PFRS surrounds the HEVs and creates a perivascular channel, which is a narrow space outside the HEV's basal lamina. The perivascular channel is the area where the circulating lymphocytes enter into the lymph nodes and lymphoid nodules.[22] FRCs are capacitated to produce extracellular matrix components such as fibronectin, collagen IV, and laminins and help in forming the thick basal lamina of HEV. Apart from the description mentioned above, HEV provides the microscopic identification as tall cuboidal endothelial cell lining, surrounded by thick basal lamina and sheath of FRC. The functions of the cellular structures of HEV are summarized in Table 1.

Molecular Mechanisms Involved in Lymphocyte Migration Through High Endothelial Venules

The endothelial cells express cell-specific surface receptors, peripheral node addressins (PNAds), and Lewis(x) ligands that attach to the L-selectin cell surface molecules on lymphocytes thereby helping in immigration into the cortex.[13,23] Generally the resident T cells need an intimate contact with the dendritic cells or the antigen-presenting cells (APCs) so as to provide the adaptive immune response. The APCs get triggered on contact with the antigen and traverse through the afferent lymphatics. Meanwhile, the T cells scrutinize the HEVs as a programmed schedule for the activated APCs-antigen complex.[24] HEVs are stimulated even in the mild inflammatory activity and immunization, thus promoting the recruitment of lymphocytes. During inflammation,

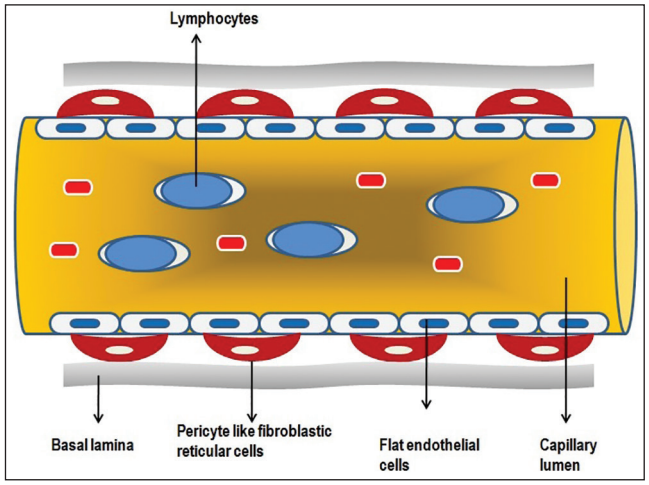

Figure 2: Longitudinal section of high endothelial venule showing luminal wall lined by endothelial cells with basal lamina and pericytes. Circulating lymphocytes are in the central stream of the capillary lumen

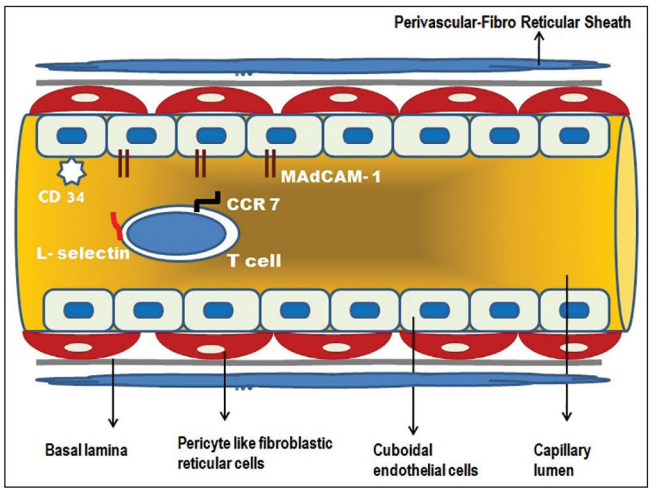

Figure 3: Longitudinal section of high endothelial venule showing luminal wall lined by cuboidal endothelial cells and covering perivascular fibroreticular sheath. The molecules MadCAM=1, CD34 attached to the luminal wall interacts with the circulating T lymphocytes

Table 1: Functions of cellular and molecular structures identified in high endothelial venules

Histological structure of high endothelial venule	Histomolecular substances that are produced	Function
Endothelial cells	Chemokines and tissue specific adhesion molecules	Selective permeability of circulating lymphocytes to the lymph node and lymphoid nodules
Pericytes	Fibroblastic reticular cells (FRCs)	Perivascular fibroreticular sheath (PFRS) Extracellular matrix produced from FRC helps in formation of basal lamina
Basal lamina		Maintains the integrity of inner endothelial cells

the chemical mediators such as monocyte chemo-attractant protein 1 (MCP-1) and interleukin 8 (IL-8) are carried to the nearest lymph node. Elongated fibroblastic reticular cells (FRCs) in the peripheral reticular meshwork capture the antigen and the chemical mediators in the lymph to form a complex. The vesicular cells around the capsular sinuses have numerous vesicles, which help in the transport and transcytosis of this bound complex and present it to a conduit system. This influences both the HEVs and the immigrating lymphocytes.[25]

These chemical molecules stir up the surface adhesion receptors of the endothelial cells in HEVs for recruiting lymphocytes. Meanwhile, influence on transformation and uphold from squamous to the cuboidal height of these endothelial cells is also regulated. The migrating lymphocytes with antigenic complex are crowded in the high endothelial vessels; during this migration period the endothelial cells of HEV predispose to the transformation of plump-cuboidal shaped to flattened endothelial cells. Persistent chemical mediators boost the height of the endothelial cells and the numeral of HEVs.[26]

Activation of T cell subsets and clusters inside the LN is an essential aspect to attain control over the mounding infection. Molecular level adaptation is necessary in HEVs. They express mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1), intercellular cell adhesion molecule (ICAM), cluster differentiation 34 (CD34), and chemokine C-C motif ligand 21 (CCL21). The T cells express C-C motif receptor 7 (CCR7), L-selectins, and lymphocyte function associated antigen-1 (LFA-1). T cells while rolling over the HEV cells are slowed down by MAdCAM-1 and CD34 that bind to L-selectin forming a weak bond. Later the CCL21 is activated and binds to CCR7 on T cells. This leads to confirmed changes in LFA-1 and a strong bond with ICAM-1 is assured. Then the T cells undergo diapedesis into the LN stroma.[27]

High Endothelial Venules in Cancer Metastasis

The progression of the primary tumor cells to a different site occurs through the lymphatic vessels. The tumor cells are carried to the sentinel LN, which is an initial step in the cascade of metastasis. The primary tumor provokes the morphological and functional changes in the lymphatic and vascular environment of the sentinel lymph node. Changes in the vascular network lead to upgradation of HEVs and lymphocyte trafficking, which creates a soil for the forthcoming events, thus paving the way for incoming tumor cells.[28]

Most commonly these tumor cells follow the stepwise pattern or pathway from the primary tumor site to the sentinel lymph node but in 20% of cases, the tumor cells evade the usual pathway and enter the central circulation leading to distant metastasis best elucidated in breast carcinomas. In the event of tumor cell circulation and lodgement in a distant site, HEV supports the neoangiogenesis, thus contributing to the regulation of metastatic process.[29] Lymphocytic trafficking is observed even in immunization but there is a minor difference in tumor cell immigration with associated lymphadenopathy. This is observed even in a few murine model studies, which is similar to dendritic cell movement during immunization.[20] Studies have suggested that the cytokines acting as messengers are released by the tumor cells and they accentuate angiogenesis and lymphangiogenesis. The structural evidence of the terminal lymph channels and vessels lack shear resistance, scarce basement membrane, and more intercellular spaces that carve the path of metastatic cells toward the lymphatic vasculature. The vascular endothelial growth factor family (VEGF-A,C,D) impose faster growth of lymph vessels, along with blood vessels. VEGF-C is a potent molecule in facilitating lymphangiogenesis anticipating the future metastatic cluster.[30,31]

Morphological alterations were observed in ultrastructural studies with HEVs showing thick basal lamina, prominent perivascular sheath, and narrow lumen when the tumor nest is far away from the HEVs. The tumor cells at that moment present with gap junctions and more tonofilaments in their cytoplasm. There is a functional remodeling when the signals for the metastatic deposit are nearing HEVs. HEV proliferation rate is highest around the metastatic tumor nest, with a thin basal lamina and enlarged lumen engorged with red blood cells providing an evidence of potential nourishment to the incoming metastatic faction. Decreased gap junctions and microvilli formation are is noticed on the tumor cell surface. This helps them to shed off easily from the nest and bond along the HEVs, thus creating an alternative pathway to metastasize into the LN with a functional resemblance to lymphocyte trafficking.[31]

Molecular Studies of High Endothelial Venules In Benign and Malignant Oral Cancers

Molecular changes in HEV in oral lesions are not extensively studied in oral benign and malignant lesions. The studies that were identified in our search in the Pubmed database are summarized in Table 2. Shen *et al*. in 2014 mentioned that remodeled HEV undergoes a series of morphological and functional changes in OPSCC progression and correlated it with metastasis.[32]

Table 2: Reported molecular studies of high endothelial vessels in benign and malignant lesions of oral cavity

Study sample tissue	Study results	Reference
Oral and pharyngeal squamous cell carcinoma	Series of morphological and functional changes of HEV‡ in disease progression and correlated with metastasis	10
Warthin's tumor	Positive expression of PNAd† in lymphoid stroma of tissue, and significant expression was observed in T lymphocytes suggesting that lymphocytes in tumor stroma are recruited by HEV	11
Sentinel lymph nodes of oral squamous cell carcinoma	Higher expression of HEV in sentinel lymph nodes regardless of the metastatic status	12
Hyper plastic intraparotid lymph node	Pathologic examination of hyperplastic intraparotid lymph node tissue showed the presence of high endothelial venules and suggested the possibility of development of Warthin's tumor	13
Neck dissected squamous cell carcinoma samples	Preferential binding of malignant cells with HEVs suggesting that venous route is an alternative metatstatic pathway	14

‡HEV = High endothelial venule, †PNAd = Peripheral node addressin

Ohya *et al*., in 2013 mentioned that lymphocytes are most likely recruited in Warthin's tumor through HEVs by normal lymphocyte homing mechanism. The study demonstrated the expression of PNAd by S1 and S2 monoclonal antibodies, and the positivity was specifically found in relation to T lymphocytes.[33] Chung *et al*. in 2012 study observed a higher expression of HEV in tumor tissue regardless of metastases of the sentinel lymphnode.[34] Terada in 2008 reported and revealed the presence of HEVs in the reactive hyperplastic intraparotid lymph nodes and suggested that Warthin's tumor may develop in intraparotid hyperplastic LN at the inception of its tumorigenesis.[35] Ivanov *et al*. in 1999 studied the neck dissections of OPSCC tissues and revealed that malignant cells preferentially bind to HEV within cervical LN sections more than adenocarcinoma cells. The study report concluded that HEVs may act as an alternative metastatic pathway in OPSCC cases.[36] HEV-like structures associated with lymphoid cell aggregates are termed as tertiary lymphoid organs (TLOs). These structures are initiated by infectious conditions, autoimmune disease process, or other pathological conditions. HEV-associated genes are GlyCAM-1, GlcNAc6ST2, autotaxin, CCL21, Mac25, DARC, and lymphotoxin beta and are required for the homeostatic control of HEV differentiation and function. These genes are triggered upon antigenic exposure in the host system and it leads to the formation of HEV-like structures in pathological conditions.[37,38] Mouse model study of ectopic lymphoid neogenesis induced by chronic inflammation expressed several HEV-associated molecules including PNAd, MADCAM-1, CXCL13, CCL19, and CCL21. Hence, this suggests that HEV could be identified in nonlymphoid tissues activating inflammatory signaling. The study results provided a feedback that lymphoid chemokines and inflammatory signaling pathways are sufficient to induce the formation of HEV.[39,40] However, another study suggested that morphogenetic differentiation of normal vessels into HEV appears to occur independently and does not require lymphokines, as they investigated in mice models deficient with T cells and B cells.[41]

Tumor Immunotherapeutic Application of High Endothelial Venule

Tumor angiogenesis is usually considered as an indicator of the tumor growth and poor prognosis.[42] However, HEV present within the tumor microenvironment may be associated with favorable prognosis.[43,44] This is because of the fact that HEV in the tumor appears to facilitate tumor destruction by allowing higher levels of lymphocyte infiltration into tumors.[45] Infiltration of native, memory, cytotoxic, and activated T cell may facilitate the destruction of tumor cells and generation of memory T cells that limit tumor metastasis.[46] Studies suggested that high densities of tumor HEV were associated with longer disease-free and metastasis-free survival of the patients. Antitumor metastasis effect was demonstrated in a study on the treatment of melanoma with tumor-specific antibody-LT alpha fusion protein-induced PNAd$^+$ HEV-like blood vessels and tertiary lymphoid organs resulted in the induction of tumor-reactive T cells, eventually leading to the eradication of pulmonary metastasis and cutaneous tumors.[47] Direct injection of modified dentritic cells in intratumoral lymphoid structures resulted in the secretion of CCL21 and hence, tumor regression.[48] Further understanding of the genes and transcription molecules associated with HEV will help to develop novel effective tumor immunotherapeutic strategies.

Conclusions

HEVs are unique structures that are identified in the lymphocytes and primarily assist in the lymphocytic migration from the blood stream in to the lymph node. Lymphocyte is a known lead aspect in the cancer metastasis. In addition to lymphocytes, the role of HEVs has been marked in recent cancer biology studies.

A comprehensive understanding of the mechanisms related to HEVs will facilitate the future research studies to develop novel therapeutic approaches in cancer patients in which lymphocytes and HEVs are considered as lead areas in metastasis.

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Conflicts of interest

There are no conflicts of interest.

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