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LYMPHANGIOGENESIS AND TUMOR METASTASIS

Eva Rovenská[1, 2], Mária Kovářová[3]

[1]National Cancer Institute of Slovakia, Bratislava, Slovak Republic
[2]National Institute of Rheumatic Diseases, Piešťany, Slovak Republic
[3]University of South Bohemia in České Budějovice, Department of Public and Social Health Care, České Budějovice, Czech Republic

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Abstract
The review article is focused on lymphangiogenesis and on metastatic spread of tumor cells via the lymphatic vessels. Numerous new lymphatic vessels (especially lymphatic capillaries) are formed in the tumors and in their nearby location during lymphangiogenesis. Tumor cells can enter the lymphatic capillaries through existing specially opening connections in the capillaries walls between their endothelial cells. These are not connected with connecting complexes. When opened, the opening is a few micrometers wide. These specialized connections are named the same as the primary valves. Tumor cells can also erode lymphatic vessels and create larger incoherence directly in their vessel wall of endothelial cells. Lymphangiogenesis is induced by vascular endothelial growth factors VEGF-C/-D and VEGF-3. On the basis of lymphangiogenesis research in experimental animals, clinical and laboratory observations in humans, some scientists suggest that anti-lymphangiogenesis treatment could be beneficial for patients who are at risk of metastases from tumors passing through lymphatic vessels.

Key words: *lymphangiogenesis; metastases; tumors; anti-lymphangiogenesis treatment*

REVIEW

Over the years, understanding and knowledge of the cellular and molecular mechanisms of lymphangiogenesis have been improving. Lymphangiogenesis is a process of creation (proliferation) of new lymphatic vessels, particularly lymph capillaries around and within the tumor. Lymphatic capillaries proliferating in the tumor are called intratumoral lymphatic vessels (ITLS) whereas peritumoral lymphatic vessels (PTLs) (Witte et al. 2006) are located around the tumor.

Over the past fifteen years, scientists have worked in basic and clinical research examining the role of lymphatic vessels in the spread of metastasis of tumors which has become a subject of increased efforts. Lymphatic vessels are part of the lymphatic immune system. In humans, the lymphatic system begins to develop between the sixth and seventh week of embryonic development, at a time when the cardiovascular system is already in place (Jeltsch et al. 2003). The system of lymphatic vessels comprises of lymphatic capillaries, pre-nodal lymphatic vessels, post-nodal lymphatic vessels. They bring the lymph to ductus thoracicus and ductus lymphaticus dexter leading into the junction of large veins. The ductus lymphaticus dexter is collecting lymph from the head and neck.

The lymphatic system consists of the following components: interstitium connective tissue, lymphatic vessels, lymphatic organs and their roving ambassadors – migrating cells (Olszewaki 1991).

The system of lymphatic vessels begins in interstitial connective tissue as lymphatic capillaries. These thin-walled vessels in their specially opening connections between their endothelial cells (Leak and Burke 1966) attach to the tissue channels located in the interstitial connective tissue. The tissue channels are components of the extravascular microcirculation (Casley-Smith 1983). The vascular microcirculation component is represented by lymphatic capillaries and blood capillaries (Rovenská and Rovenský 2011, Sato et al. 2015).

Lymphatic capillaries drain the tissue fluid, immune cells and debris from the interstitial connective tissue into the lymph nodes. Drainage is carried out by specialized connections between the endothelial cells of the lymphatic capillaries.

In 1966, Leak and Burke described (Leak and Burke 1966) the existence of specialized connection by transmission electron microscopy. Overlapping lobes of adjacent endothelial cells are present in described connections.

Desmosomes and any other coupling complexes are not found between overlapping edges or tips, therefore under increasing pressure in the interstitium, the inner tip sweeps into the capillary lumen and the outer tip is attached or affixed to the interstitial fibers, so called anchor fibers. These specialized connections in the walls of lymphatic capillaries are called primary valves (endothelial microvalves) and may be opened to such an extent to create a few microns wide opening between interstitium and lumen of the capillary. The tissue fluid, immune cells and debris is flowing through the openings from the interstitium into the lumen of the capillary (Ikomi et al. 1996, Trzewick et al. 2001, Schmidt-Schönbein 2003).

The content of cells in the peripheral and central lymph is different. Peripheral (afferent, pre-nodal) lymph contains a small number of erythrocytes, numerous lymphocytes, plasma cells, monocytes, macrophages, granulocytes and dendritic cells. Lymph is transported via lymph vessels to lymph nodes. In the lymph, there are memory lymphocytes and effector lymphocytes. The central (efferent, post-nodal) lymph contains larger amount of white blood cells, because naive lymphocytes enter the lymph from post-capillar venules that have high endothelia in the lymph nodes. Based on the microscopic image, the endothelial cells were named HEV (high endothelial venules). This phenomenon was described by Gowans and Knight (1964), and is known as physiological lymphocyte recirculation. The lymphocytes return to the blood stream with post-nodal lymph.

In 1937, Pullinger and Florey became first authors who described lymphangiogenesis in inflammation and induced it in experimental animals. Authors describe proliferation of lymphatic vessels and debris that is transported directly by the lymphatic vessels or by phagocytic cells. In 1935, under the light microscope, Pullinger and Florey had already observed tissue fibers surrounding the lymphatic capillaries, when studying the skin of experimental animals in which they induced edema of the connective tissue. Fibers are attached directly to the endothelial cells. Lymphatic capillaries are not surrounded by a basal membrane. Fibers avoid collapsing the lymphatic capillaries when edema is present. Literature also refers it to anchor fibers (anchoring filaments).

Lymphatic vessels play an important drainage function. Lymphatic drainage takes place in the interstitial connective tissue which is located almost everywhere in the body. Vandoorne et al. (2010) have visualized angiogenesis and permeability of small blood vessels and also lymphatic drainage after injecting labeled serum albumin into the blood stream of experimental animals. They used non-invasive methods for visualization of vascular permeability and lymphatic drainage. Authors emphasized that angiogenesis plays a role in the growth of tumors (Folkman 1992). During an increase of blood vessels permeability, an extravasation of macromolecules from plasma occurs, as well as the interstitial flow around the tumor and lymphatic drainage towards the draining lymph node (Vandoorne et al. 2010). Angiogenesis is required for tumor growth and metastasis (Dvorak et al. 1999). In clinical studies, authors observed a link between increased levels of VEGF (Vascular Endothelial Growth Factor) in the blood and increased metastases to the lymph nodes. On the basis of observations, it was hypothesized that suppressed high level VEGF can reduce the permeability of the blood vessels and

the lymphatic drainage towards the draining lymph node (Pullinger and Florey 1935, Vandoorne et al. 2010).

Lymphangiogenesis may actively contribute to tumor metastasis (Ji 2006a, Maeng et al. 2015, Pereira et al. 2015, Wilkie et al. 2015). Lymphangiogenesis influence growth factors, cytokines and chemokines. E.g. VEGF-C and -D (vascular endothelial growth factor C and D) induce proliferation of lymphatic endothelial cells and thus lymphangiogenesis. It was found that the cells in human melanoma and carcinoma cells in rats contain vast growth factors VEGF-C and -D. Several clinical and pathological studies have shown a relationship between the occurrence of VEGF-C and D in the tumor and metastatic spread of tumors in humans (Rubbia-Brandt et al. 2004, Ji 2006a). Chemokines and cytokines, e.g. CCL21, CCR7, play a role in addition to VEGF-C/-D in metastases spread (Zlotnik 2004, Ji 2006a, b).

Numerous models of tumors induced in animals have suggested that lymphatic capillaries located directly in the tumor may promote tumor spread to the lymph nodes. Moreover, the tumor lymphangiogenesis has been identified as a new risk factor for lymph node metastases in melanoma and skin squamous cancer of the head and neck (Dadras et al. 2003, Maula et al. 2003, Ji 2006a, Pastushenko et al. 2015, Wilkie et al. 2015). Peritumoral lymphatic vessels play also a role in the metastatic spread of tumors. Cancer cells enter lymphatic vessels (namely, lymphatic capillaries) through specially opening connections between the endothelial cells, or they can cause greater discontinuities in the endothelial cells layer (Alitalo and Detmar 2012). According to the classical view, metastasis malignant tumor cells may continue into distal lymph nodes after they had entered into the sentinel node. They are then transported from the lymph into the bloodstream and can create metastases in organs (Alitalo and Detmar 2012).

The latest scientific knowledge has outlined a development of anti-lymphangiogenesis treatment to be important for future research of tumor models in animals and humans (Ji 2006a).

It is possible that a blockade of VEGF signaling pathway -C/-D/VEGF-3 is useful as a new type of cancer treatment. The more lymphatic vessels in lymphangiogenesis develop, the more likely is that tumorous cells enter lymphatic stream and escape from the original location of the tumor (Ji 2006a).

VEGF-3 was identified to be the first molecule that is important for lymphangiogenesis (Alitalo and Detmar 2012). Increasing knowledge about the role of the lymphatic vascular system in cancer metastases enables progress in the development of anti-lymphangiogenesis cancer treatment. Targeted anti-lymphangiogenesis treatment could be administered in selected patients who are threatened by propagating metastases through the lymphatic vessels (Alitalo and Detmar 2012).

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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Contact:

Eva Rovenská, National Cancer Institute of Slovakia, Klenová 1, 833 10 Bratislava, Slovak Republic
Email: rovenska@yahoo.com