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The Induction of High Endothelial Venule Remodeling by Primary Tumors does not Correlate to the Metastatic Capability of Tumor Cells

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Abstract

The spread of cancer cells to draining lymph nodes is usually the initial step of metastasis and is the most important unfavorable prognostic factor in many types of carcinoma. High endothelial venule (HEV) remodeling in the draining lymph node induced by the primary tumor has been observed, and its molecular mechanism has been recently explored. However, such remodeling has been prematurely linked to the metastatic capability of cancer cells. Here we discuss published data on the question of whether both benign and malignant tumors with either high- or low-metastatic ability can induce HEV remodeling in the draining lymph node. A second point is that HEV remodeling and integration into the vasculature of a secondary tumor in the lymph node might facilitate further spreading of those cancer cells once they have attained metastatic capability. More efforts are needed to clarify the role of remodeled HEV in the spreading of cancer cells from an involved lymph node to distant organs.

The metastasis of cancer cells to the draining lymph nodes is usually the initial step in systemic spreading of cancer and is the most important unfavorable prognostic factor in many types of carcinoma (1-5). The molecular mechanisms inside the lymph node favorable for survival and further spreading of cancer cells remain unclear.

There is a specific type of blood vessel called the high endothelial venule (HEV) inside the lymph node. Under normal conditions, HEVs produce a specific marker protein, peripheral node addressin (PNAd), which is a ligand that is recognized by the homing receptor L-selectin expressed in the cellular membrane of naïve lymphocytes (6-8). The interaction between PNAd and L-selectin results in the extravasation of lymphocytes from the circulation into the lymphoid tissue. HEVs seldom harbor red blood cells under normal conditions, instead being focused on immune response. However, in cancer, HEVs in the draining lymph node can be remodeled under the influence of the primary tumor, resulting in dramatic dilation of the vessel lumen, significant flattening of the endothelium, and the appearance of red blood cells in the lumen (9-10). Importantly, the remodeling procedure can even precede the arrival of metastatic cancer cells in the lymph node. Further, remodeled HEVs can integrate into the tumor vasculature after metastatic cancer cells colonize in the lymph node (9). The remodeled and integrated HEVs lose PNAd and carry numerous red blood cells, suggesting a functional shift from immune response to blood flow that supports the survival and growth of the secondary tumor in the node (9-10). The remodeled HEVs in the lymph node can become "mother vessels" of the secondary tumor (9-10), but little is known about how this occurs molecularly.

In a recent article by Farnsworth and colleagues (11), bone morphogenetic protein-4 (BMP-4) was found to be expressed in normal HEV, and loss of BMP-4 correlated to more dramatic remodeling of HEVs in the tumor-draining lymph node. This is the first identified molecule with a role in tumor-induced HEV remodeling, and the evidence is strong and convincing.

The authors also suggest a link between HEV remodeling and the metastatic capability of the primary tumor cancer cells (11), but the evidence is not as robust. First, the non-metastatic control in this study was the 293 *EBNA-1* cell line. This is not a cancer cell line, but a human embryonic kidney line transfected with the EBNA-1 gene for immortalization (12). Therefore, the absence of HEV remodeling in the lymph node of the mice carrying a 293 EBNA-1 xenograft may not be a generalizable phenomenon associated with a non-metastatic tumor. Second, the difference in the HEV lumen area (an enlarged lumen being one of the indications of HEV remodeling) between lymph nodes associated with nonmetastatic and metastatic tumors shown in Figure 4B of the article is not observed in Figure 5C, in which the lumen areas of both types of lymph nodes were not statistically different (11).

In our previous study (9), we reported that HEV remodeling can be induced by primary tumors formed by high-metastatic as well as low-metastatic cellular clones, suggesting that HEV remodeling is not correlated with the metastatic ability of the cells.

In a transgenic mouse model of prostate tumor induced by inactivation of the *Apc* gene in the prostate epithelium via the *Cre*-loxP system, benign prostate tumors without metastatic ability can be successfully induced (13). In the mice bearing such benign tumors, remodeling of HEV in the sacral lymph node is evident, confirming that benign tumor can also induce HEV remodeling in the draining lymph nodes.

Collectively, both benign and malignant tumors, with either high or low metastatic character, can induce HEV remodeling in the draining lymph node. Therefore, HEV remodeling cannot be regarded as one of the aggressive characteristics of the primary tumor.

However, the integration of remodeled HEVs into the tumor vasculature could have an important role in promoting the further spread of the cancer cells. Squamous cell carcinoma cells have

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been found to preferentially attach to HEV (14), suggesting that a downstream metastatic event could be promoted by the integrated HEV in the secondary tumor vasculature. Obviously, more direct evidence is needed to support the hypothesis that HEV remodeling and integration into tumor vasculature are the main reasons for the increased distant-metastasis rate of cancer cells after their initial spread to the draining lymph node.

In conclusion, although HEV remodeling seems important to the survival and growth of secondary tumors in the lymph nodes, it does not unambiguously correlate with the metastatic ability of the primary tumor cells. More efforts are warranted to clarify the role of remodeled HEV for the further spreading of cancer cells from the involved lymph node.

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