

*Editorial***THE ROLE OF THE LYMPHOVASCULAR SYSTEM  
IN CANCER METASTASIS**

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Nodal status is the most important prognostic indicator for patients' outcomes with solid cancer. The physiologic definition of a sentinel lymph node (SLN) by Morton et al (1) in 1992 ushered in a new era to target the SLNs for assessing the status of the draining nodal basin from the primary cancer site. Micrometastasis is a strong prognostic marker for melanoma (2) and breast cancer (3), but the therapeutic benefit of removing a positive SLN has yet to be demonstrated (2,4). The concept that, in general, cancer cells from the local tumor microenvironment spread to the regional SLNs first then beyond to the systemic sites, has been well established in melanoma and breast cancer and is being tested in other solid cancers including cancers of the head and neck, gastrointestinal tract, genitourinary tract, gynecological sites and the lung (5). The Nature milestones on cancer (<http://www.nature.com/milestones/milecancer/timeline.html>) have summarized major developments of cancer metastasis since the "seed and soil" theory of Paget (6). It is well accepted that cancer development is a genetically driven process with progression within the tumor microenvironment to distant body sites, often through the gateway

of the SLNs. However, in a minority situation (~20% of the time), the cancer cells may spread through the blood vascular system to the distant sites bypassing the SLNs (5).

Thus, cancer progression is most consistent with Hellman's spectrum theory (7). This theory states that for any given malignant lesion, development of nodal and systemic metastasis from localized disease is a progressive process. The challenge is to identify patients with truly localized disease versus those patients with metastasis to the nodal and/or systemic sites. It is critical to understand the process of lymphangiogenesis and hemangiogenesis in the tumor microenvironment regarding the initial steps of cancer cells entering into the lymphatic and vascular systems (8-12). Furthermore, it is important to define the spread of cancer cells through the lymphatic system (incubator hypothesis) or simultaneously through the lymphatic and blood vascular system (marker hypothesis) (5,13) on a molecular basis so that rational therapy can be developed to curb the process of specific routes of metastasis. The melanoma model has been described to illustrate these patterns of metastasis (14). Whether the lymphogenous or hematogenous spread of cancer is independent or interconnected has not been conclusively determined to date. For these

reasons, the role of the lymphovascular system in cancer metastasis has been scrutinized in three previous international symposia in 2005, 2007, and 2009, sponsored by the Sentinel Node Oncology Foundation and the National Cancer Institute so that a rational basis for therapy can be developed (15-17).

Future studies should be directed to the spectrum of tumor burden in the primary tumor, in the initiation of local invasion, and lymphatic versus vascular spread or both. The clinical significance of micrometastasis in the SLNs also needs to be further defined in relationship to its potential to spread beyond the SLNs to the distant sites (6,18). The role of immune responses to cancer spread has been extensively studied, but the conditions for immune reactivity against cancer and cancer escape through immune suppression are still not clearly understood (19). Occasionally, distant metastasis develops following resection of the primary cancer or nodal metastasis and in some instances, there is a long period of dormancy, which remains incompletely understood (20). The complex molecular mechanisms of cancer metastasis through the lymphovascular system still remains to be further deciphered. In addition, great heterogeneity is noted within the same type of cancer, which can contain multiple clones using different metabolic pathways to proliferate and spread and within different subgroups of cancer patients where gene profiles and biomarkers may be useful to offer more selective and effective personalized therapy (21-22). Thus, further secrets and implications remain hidden in the SLN that have barely begun to be explored.

In summary, cancer metastasis is a continuum from its inception in the tumor microenvironment through its progression to spread to distant sites by way of the lymphovascular system, oftentimes in an orderly fashion via the SLN gateway. Cancer metastasis is progressive, and early detection remains key to successful eradication. Basic scientists from multiple disciplines and clinicians from various specialties including

oncology, surgery, pathology, radiology, and lymphology need to come together for fruitful and focused translational interactions at the International Congresses of Lymphology (23) (September 19-23, 2011, Malmö, Sweden – <http://www.lymphology2011.com>), and the International Symposia on Cancer Metastasis and the Lymphovascular System: Basis for Rational Therapy (24) next in May 11-14, 2011, in New York City. Cross-fertilization of fresh ideas among these disciplines and encouragement of investigations between young and senior investigators should enhance the translation of basic science into clinical application and further challenge basic scientists to address more fully the vexing clinical issues and provocative unanswered questions by linking “the bench to the bedside and community” (25).

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