# Lymphangiogenesis in Cancer: A Review

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inflammatory arthritis per se [18], chronically inflamed tissue [19], inflamed lymph nodes [20], ovarian folliculogenesis [21], and dendritic cell migration [22]. However, I propose to develop this review largely on lymphangiogenesis in respect of cancer proper with special reference to the quest for therapy.

Concerning cancer therapy in general, Poste [23] in 1986 rang the bell of "increased use of human tumor cells to replace rodent cells system." As he stressed, "Advances in molecular biology offer exciting prospects for the identification of new therapeutic targets." In sum, he advocated the development of "new knowledge about the cell biology of metastasis."

This hope is being realized in the expanding field of lymphangiogenesis. Thus, with regard to fibroblast growth factor receptor (FGFR), Larrieu-Lahargue [24] and colleagues provided evidence that targeting FGFR signaling may be an interesting approach to inhibit tumor lymphangiogenesis and metastatic spread."

From all over the world, the clarion call is for identifying and using the molecular regulators of lymphangiogenesis [25–37]. Incidentally, progress is being made as regards identification of biomolecules that predict response to treatment [38] and identification of potentially important prognostic biomarkers [39]. In like manner, attention has been focused on insertion of radiolabeled biomolecules into cancer cells for imaging or targeted Auger electron radiotherapy of malignancies [40]. Models must take into account certain nuances such as the fact that the species, conformers and structures of biomolecules are very sensitive to their environment and aggregation state [41]. Fortunately, the recent research on novel markers for lymphatic endothelial cells has been identified and their availability has revolutionized research in the field [42].

Karpanen and Alitalo [43] noted that, despite significant achievements, "Several key questions remain to be resolved, including the relative contributions of different pathways targeting lymphatic vasculature, the molecular and cellular processes of lymphatic maturation, and the detailed mechanisms of tumor metastasis via the lymphatic system." One group [44] presented "a significantly more detailed view and novel model of early lymphatic development." Actually, vascular endothelial growth factor (VEGF)-C has been identified as a molecular link between tumor lymphangiogenesis and metastasis [45].

The intervention and targeting of the FGF-2- and of VEGF-C-induced angiogenic and lymphangiogenic synergism could be potentially important approaches for cancer therapy and prevention of metastasis [46]. Similarly, "Immuno-PET with lymphatic-specific antibodies may open up new avenues for the early detection of metastasis, and the images obtained might be used as biomarkers for the progression of diseases associated with lymphangiogenesis" [47]. Concerning Sphingosine-I-phosphate (SIP), Yoon et al. [48] concluded that "Our results suggest that SIP is the first lymphangiogenic bioactive lipid to be identified and that SIP and its receptors might serve as new therapeutic targets against inflammatory disease and lymphatic metastasis in tumors." Elsewhere, [49] this was confirmed for breast cancer. Actually, "blockage of PDGF-induced lymphangiogenesis may provide a novel approach for prevention and treatment of lymphatic metastasis". Indeed, as Christiansen and Detmar [50] concluded, "The progression of our understanding from the lymphatic system as a somewhat passive conduit for metastasis to an active participant in metastatic tumor dissemination is regulated by a complex array of lymphangiogenic factors, chemokines, and immune cell subsets".

## Discussion

Having reviewed lymphangiogenesis and cancer above, it remains to tackle two fronts. Firstly, I have hypothesized that lymphangiogenesis explains the age-old puzzle that lung cancer selectively attacks the adrenal glands [51]. What of other puzzles? Secondly, let me hypothesize with regard to the giant lymphatic conduit, i.e., the thoracic duct. As far back as 1798, the great Cooper [52] vouched that this organ is important to the human economy. As I see it, part of the difficulty of carrying out research on it is because of its sheer length of some 45 cm. Hitherto, trouble was taken laboriously to investigate it with numerous cross-sections [53,54].

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[70,71]. Moreover, it is to be noted that there are results which "reveal further functional differences between VEGR-D and VEGF-C" [72,73]. Again, Nagy's group [74] remarked that "These findings raise the possibility that similar abnormal lymphatics develop in other pathologies in which VEGF-A is overexpressed, e.g., malignant tumors and chronic inflammation." On their part, Wong's associates [75] wrote, "These results suggest that tumor-secreted VEGF-C and, to a lesser extent, VEGF-A, are important for inducing prostate cancer intratumoral lymphangiogenesis but are unnecessary for lymph node metastasis." Likewise, Schoppmann's co-workers [76] were definite: "In conclusion VEGF-C-expressing TAMs play a novel role in peritumoral lymphangiogenesis and subsequent dissemination in human cancer." In like manner, Susanne Jackowski's [76] associates wrote at length thus: "The detection of molecules that are relatively specifically expressed by lymphatic endothelial cells, like podoplanin, lymphatic vessel endothelial hyaluronate receptor 1 (LYVE-1), vascular endothelial growth factor receptor (VEGFR)-3, prospero-related homebox gene PROX-1, desmoplakin-1(2.17), and B-chemokine receptor D6, has facilitated new insights into the molecular mechdevelopment." Indeed, as they stressed, "Two……..cells."

These ideas have been entertained largely through the characterization of animal models. In contrast, I have offered elsewhere a dozen human models for cancer research [76]. Here, I acknowledge that the biology of lung cancer has long been linked with biological properties inherent in the tumor cells themselves [77]. I am suggesting, finally, that the human thoracic duct's microenvironment probably holds the key for decoding Nature's secrets through (i) recondite retrieval of necrotic cancer cells commingled with erythrocytes, and (ii) transparent translational research on them. Is there a biomolecule lurking? Be that as it may, when the much expected breakthrough materializes, mankind's "War on Cancer" [78,79] will be won sooner than later!

## References


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