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Lymphangiogenesis in Cancer: A Review

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Abstract

Lymphangiogenesis, the new formation of lymph vessels, has recently matured as a leading research front although recorded personally by the author in 1963. This review deals with its molecular parameters, especially as regards possible target therapy of cancer. Finally, it is suggested that the microenvironment delineated by a special longitudinal method of study of the thoracic duct is naturally programmed for that translational elucidation whose success is probably but a matter of time.

Keywords: Lymphangiogenesis; Cancer; Lymph vessels; Lung cancer

Introduction

Lymphgangiogenesis has nowadays been admitted to much vibrant existence. "In recent years," said Huang and associates, [1] "the pathological roles of lymphangiogenesis, the generation of new lymphatic vessels from preexisting ones, in inflammatory diseases and cancer progression are beginning to be elucidated." It is to be noted that they began their review with the phrase: "In recent years."

Years ago, exactly from 1957, I began to publish on the metastases of lung cancer [2]. I had been struck by them during the autopsies which I had watched or was allowed to perform in Scotland at the great Glasgow Western Infirmary [3]. Before long, other publications followed [4–8]. And, by 1959, I came across the 4th paper in a series of animal experiments carried out by Zeidman [9]. He injected cancer cells into the pelvic lymphatics of a number of rabbits. He was surprised to observe that the topography of the resulting secondary deposits in retrogradely-situated popliteal nodes was such that the pathways for tumor transportation were newly formed collateral channels and not the preexisting efferent vessels. He comfortably concluded that, with regard to the popliteal node of the rabbit, the newly formed channels functioned as afferent vessels and conveyed tumor emboli to the peripheral sinuses rather than to the hilar areas, where their lodgment would have occurred had they been transported retrogradely by way of the animal's pre-existing efferent vessel.

On receiving the requested reprint, I set to work. In fact, having personally introduced the mono-block formalin-fixation method [10], I found that there was panoramic diminution in size of the lymph nodes metastasized in the abdomen [11]. Much as the current view then was that such spread was by way of retrograde access through the lymph vessels [12], it occurred to me to actually trace their footsteps in my collection. In particular, retrograde carriage should lead to earliest deposition in the concave area, i.e., the exit position. However, this was not occurring, seeing that the initial deposits were found in the convex area, i.e., the access position. I promptly reported this discovery [13]. In particular; I used the expression "new" formation. Indeed, it occurred six times as follows:

- Newly formed afferent vessels
- New afferents open up
- Newly-opened backwardly-directed lymphatics
- New retrogradely-directed afferent lymphatics
- New afferent lymphatics links
- Probably most often transported backwards by way of newly formed afferent lymph vessels

Unfortunately, the title of my paper focused on challenging the "retrograde" theory. Perhaps, from hindsight, I should have employed another title: "New formation of lymph vessels during abdominal lymph node metastasis." Be that as it may, its acknowledged name of "lymphangiogenesis" has come to stay. However, in this context, I wonder who first used this precise name in a scientific communication as regards the phenomenon itself.

The Current Language

For a start, instances of early or first usage are worthy of documentation. Please note this example: "Lymphangiogenesis has recently gained attention for its potential involvement in lymphatic dissemination and metastasis of tumor cells". This was from Koyama's group [14]. Note also that they cited 45 articles beginning from 2002 to 2007, 14 of them being specifically on lymphangiogenesis. Incidentally, their work was based on experimental mouse models and their emphasis was on hyaluronan, a major extracellular constituent. As they concluded, "These findings underline the significance of tumor-associated stroma in the promotion of intratumoral lymphangiogenesis and suggest a pivotal role for the hyaluronan-rich tumor microenvironment". Co-authors14 who were based in Greece and Austria stated that lymphangiogenesis "recently became a new research frontier," and cited five references from the 2002 to 2004 period. As they concluded, "the mechanisms of lymphangiogenesis (were) triggered by the discovery of specific lymphatic endothelium markers, such as podoplanin, LYVE-1 and VEGF-3".

The Current Parameters

Incidentally, lymphangiogenesis is playing a vital role in such mundane matters as chronic allergic inflammation [15], chronic inflammatory wounds [16], chronic inflammatory arthritis [17],

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].

On the contrary, because of introducing the mono-block formalin-fixation method, I was able to investigate the full axial specimen from the neck to the pelvis [10]. This was possible thanks to my late teacher, Professor D. F. Cappell. That was when the present-day crisis on research using human tissues had not yet reared its ugly head [55]. Owing to serendipitous coiling of the entire thoracic duct in Swiss-roll fashion, I was able to study each duct with just one microscope slide [56]. Propitiously, there was a major conclusion concerning the panoramic picture of the lung cancer cells cruising in it at the moment of death. It was cutely specific thus:

"Necrosis of the cancer cells was apparent in 3 cases, but it was clear that this had occurred in association with large aggregates of the malignant cells and that among such aggregated cells red blood corpuscles abounded."

Subsequently, I theorized that this natural phenomenon should be explained on the basis of a hitherto hidden factor [57]. The beauty of this factor that I have named as the "Erythrocyte Associated Necrosis Factor" (EANF) is that it is readily open to translational research [58]. All that is required is to carry out on consenting patient's ductal cannulation not just ordinarily [59] but with the intravital video microscope [60]. This should be comparatively easy because the scientifically important subsets of necrotic cancer cells and lively cancer cells are there for recondite retrieval. Moreover, lung cancer is the burgeoning burden on mankind, especially males [61]. Fortunately, there is for this suggested research no want of patients.

Incidentally, the "necrosis" apparent among the metastasizing cancer cells in the thoracic duct is a far cry from the "Tumor Necrosis Factor" which has long been promoted in the literature [62-64]. In other words; a point needs to be made. It is that this particular factor belongs to the primary tumor itself. On the other hand, the EANF manifests during the actual metastasis process. Indeed, this manifestation occurs definitely even before deposition in the secondary site let alone during colonization in such a site proper.

Conclusion

To sum up, I have reviewed above the parameters of lymphangiogenesis with reference to cancer. Perhaps, I should mention in passing the various intimidating factors noted by the researchers in the important field of lymphangiogenesis. There is first the lymphatic marker VEGFR-3 and growth factor VEGF-C [65-68], VEGF-C being a paracrine factor [69]. There is also the chain whose responsiveness is enhanced through preexisting lymphatic endothelium by VEGR-3 binding factors, VEGR-C and VEGF-D

[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!

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