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EDITORIAL

LYMPHANGIOGENESIS REVIEWS, LYMPHOLOGY, AND MEDICAL IGNORANCE

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ABSTRACT

Lymphology *is launching a* Lymphangiogenesis Reviews *series focusing on unanswered, unasked, and perhaps wrongly answered questions (medical ignorance). The Journal's historic role, along with ISL Congresses and many ISL lymphologists – past and present – in bringing the phenomenon of lymphangiogenesis to light is emphasized.*

Keywords: lymphangiogenesis, hemangiogenesis, angiogenesis, lymphology, medical ignorance

Beginning with the March 2006 article (1) on the impact of transgenic technology on discovery of lymphangiogenesis genes and continuing in this issue's feature by Sleeman on tumor lymphangiogenesis (2), *Lymphology* is hosting an ongoing series of timely up-to-date *Lymphangiogenesis Reviews* by experts who have a special talent for exposing what we don't know (unanswered, unasked, and perhaps wrongly answered questions, i.e., ignorance) as well as what is known (what we think we do know) about lymphatic development, growth, and repair under normal physiologic conditions and during disease processes and how this knowledge (and ignorance) can be translated into advances in management of patients and prevention of lymphedema and other lymphatic system disorders.

It is indeed fitting that *Lymphology* and the International Society of Lymphology (ISL) should lead this endeavor for it was in these pages during the 1980's (3-5) and in an ISL thematic symposium during the 4th World Congress of Microcirculation in Tokyo in 1987 "Are Lymphatics Different From Blood Vessels?" (6) that the term "lymphangiogenesis" was introduced along with "lymphvasculogenesis" and "lymphangiotumorigenesis" (as distinguished from their counterparts in the blood vasculature – "bloodvasculogenesis" or "hemvasculogenesis" and "hemangiotumorigenesis"). This more precise terminology and special focus on lymphangiogenesis became a regular feature during subsequent ISL Congresses as lymphologists from around the world explored together lymphatic endothelial biology and lymphangiogenesis *in vitro*, embryonic development, disease pathogenesis, syndrome classification, and potential therapeutic approaches, while also providing live consultations for patients afflicted with lymphangiogenic/lymphvasculogenic disorders. Attention was specifically directed to the following: "lymphangiotumorigenesis" manifesting in the daunting childhood

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angioadenodysplasias and the hallmark lymphatic derived-Kaposi sarcoma of the emerging AIDS pandemic (7); useful new techniques and refined macro- and micro-imaging modalities to dynamically delineate and differentiate lymphangiogenic processes restoring lymphatic continuity or gone awry; pathogenetic mechanisms and syndromic classification of developmental including genetic disorders of the lymphatic system (8); and potential anti- and pro-lymphangiogenic and anti-angiotumorigenic therapeutic approaches, including pharmacologic lymphangiomodulators, interventional catheter ablation, and operations.

"Tumor lymphangiogenesis" was the subject of a *Lymphology* editorial in 1997 (9) at a time when leading "angiogenesis" (i.e., hemangiogenesis) experts still doubted its very existence. Sleeman's *Lymphangiogenesis Review* in this issue (2) and Pepper's unanswered questions in an earlier *Lymphology Commentary* (10) update the controversy and place relevant knowns and unknowns on tumor lymphangiogenesis in perspective.

In 1997, *Lymphology*'s Editors authored the first chapter reviewing the subject of "Lymphangiogenesis," which appeared in Goldberg and Rosen's tome on *Control of Angiogenesis* (11). Interestingly, at the time it was written (1995-96), the first lymphatic growth factor VEGF-C had not yet been discovered and its receptor VEGFR3 had not yet been linked to lymphatic system growth, i.e., there was not yet a solid molecular foundation for lymphangiogenesis. Even the word "lymphangiogenesis," was still unfamiliar. But the phenomenon – growth and regrowth of lymphatic vessels – had clearly fascinated many lymphologists for a long time. The chapter traced this century-long continuum of observations and contributions from such thought leaders as Sabin, Kampmeier, Huntington, Clark and Clark, Pullinger, and Nobelist Florey long before the formation of the ISL in 1966, through the pages of the leading lymphology texts by ISL pioneers Courtice, Yoffey, Földi, Szabo, and Kinmonth, and subsequently in presentations in ISL Congresses and publications by ISL basic scientists and physicians (including Clodius, Olszewski, Johnston, Gnepp, Leak, Hay, and Papendieck, among many others).

The rapid evolution of "lymphangiogenesis" into a "hot topic" over the past decade with the discovery of lymphatic growth factor ligands, endothelial receptors, transcription factors, and genes, has been described in numerous recent reviews of the subject in leading scientific journals, thereby exposing a large general biomedical audience to the wonders and puzzles of lymphatic growth and development. But it is nonetheless valuable at this juncture to reflect on the contributions of lymphologists, *Lymphology*, and the ISL, to the birth of this field and the realization of how much further we have to go to understand fully and translate these advances into the clinical arena (12). While some of the progress to date has predictably and systematically flowed from bench nearly to bedside, e.g., VEGF-C/VEGFR3, still other discoveries, e.g., FOXC2 gene mutations in lymphedema-distichiasis syndrome (13) and angiopoietin 2 knockout mice with chylous ascites rescued by angiopoietin-1 knock-in (14), have identified at first blush surprising lymphvasculo/angiogenic factors and regulatory genes, suggesting more circuitous and complex molecular signaling pathways and crosstalk (1).

Finally, our emphasis in *Lymphangiogenesis Review*s will not be on exhaustive literature analyses but rather on medical ignorance and the expanding universe of unanswered questions. It is this terrain which will form the next frontier in lymphangiogenesis research.

REFERENCES

1. Suri, C: The emergence of molecular and transgenic lymphology: What do we (really) know so far? Lymphology 39 (2006), 1-7.

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2. Sleeman, JP: The relationship between tumors and the lymphatics: What more is there to know? Lymphology 37 (2006), 62-68.
3. Lymphology 17 (1984),15-22. Cystic hygroma reconsidered: Hamartoma or neoplasm? Primary culture of an endothelial cell line from a massive cervicomediastinal cystic hygroma with bony lymphangiomatosis.
4. Lymphology 19 (1986), 21-28. Lymphangiogenesis and lymphologic syndromes.
5. Lymphology 20 (1987), 171-178. Lymphatics and blood vessels, lymphangiogenesis and hemangiogenesis: From cell biology to clinical medicine.
6. Lymphology 20:167-276, 1987. *Are Lymphatics Different From Blood Vessels?* 4th World Conference on Microcirculation Symposium.
7. Lymphology 21 (1988), 1-87. Symposium on *AIDS, Kaposi's Sarcoma, and the Lymphatic System: The Known and the Unknown*.
8. Lymphology 26 (1993), 156-168. Developmental disorders of the lymphatic system.
9. Lymphology 30 (1997), 1-2. On tumor (and other) lymphangiogenesis.
10. Pepper, MS: Lymphangiogenesis and tumor metastasis: More questions than answers. Lymphology 33 (2000), 144-147.
11. Witte, MH, DL Way, CL Witte, et al: Lymphangiogenesis: Mechanisms, significance and clinical implications. In: *Regulation of Angiogenesis*. Goldberg, ID, EM Rosen (Eds.), Birkhäuser Verlag Basel/Switzerland 1997, pp. 65-112.
12. Witte, MH, M Ohkuma, M Andrade, et al: *Nature*'s historic gap: The 20th century of lymphology. Lymphology 38 (2006), 157-158.
13. Fang, J, SL Dagenais, RP Erickson, et al: Mutations in FOXC2 (MFH-1), a forkhead family transcription factor, are responsible for the hereditary lymphedema-distichiasis syndrome. Am. J. Hum. Genet. 67 (2000), 1382-1388.
14. Gale, NW, G Thurston, SF Hackett, et al: Angiopoietin-2 is required for postnatal angiogenesis and lymphatic patterning, and only the latter role is rescued by angiopoietin-1. Developmental Cell 3:411-423, 2002.

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