

## EDITORIAL

## ON TUMOR (AND OTHER) LYMPHANGIOGENESIS

In a recent exchange on tumor angiogenesis in the *New England Journal of Medicine* (1,2), the question was raised and debated on whether intratumor lymphatics are present, "functional," newly formed, and contribute to the tumor microvascular index (a postulated correlate of tumor aggressiveness). In response to Folkman's assertion that tumors do not possess lymphatics, Van Netten et al (1) review the contrary evidence that tumors, and specifically breast cancers, display at least lymphatic-like labyrinths. They further propose the term "lymphagenesis," an unfortunate choice literally meaning absence of lymph formation (i.e., lymph *agenesis*) or alternatively, formation of lymph fluid (i.e., lymph *a* genesis). In 1986, we introduced the terms "lymphangiogenesis" and "hemangiogenesis" to distinguish lymph vessel from blood vessel formation—terms consistent with the nomenclature of angiotumors [lymphangioma-hemangioma (sarcoma)] and reflecting the lymphatic functional unit, the "lymphangion" (4,5).

The discovery of the lymph vessels and the concept that blood circulates (by Aselli and Harvey, respectively), took place in the early 17<sup>th</sup> century. By the early 1900's, the phenomenon of lymphatic growth and regrowth became a subject of intense interest. Sabin proposed that lymphatics originate as buds from the venous system (centripetal theory) whereas Kampmeier favored an independent origin from tissue mesenchyme (centrifugal theory), an issue still unresolved (reviewed in 5). Later, lymphatic regeneration

was vividly displayed by *in vivo* microscopy and microlymphangiography during inflammation, abscesses, and wound healing (reviewed in 5). Intratumor lymphatics were also identified in cancers (e.g., melanoma, intestinal malignancy, and breast carcinoma) but it was not known then, and indeed is not yet clear, whether these lymphatics are residual, newly formed, obstructed, malformed, or labyrinthine (5,6).

More recently, misleading nomenclature such as "vasculature and the lymphatics" and unprefixing "angiogenesis" have confused the issues and further marginalized the neglected lymphatic vasculature and its disorders. Nonetheless, despite ultrastructural and functional differences, the similarities both *in vivo* and *in vitro* between lymphatics and blood vessels and their respective endothelia far outweigh the differences (5,7). Thus, Dumont (8) challenged the use of conventional endothelial markers such as Factor VIII-related antigen (von Willebrand factor) and Weibel-Palade bodies to distinguish tumor microvessels of lymphatic from blood vessel origin. Indeed, tumor microvessels—hyperpermeable, sinusoidal, and labyrinthine—resemble lymphatics more than typical blood vessels, further suggesting an indeterminate mixture of embryonic vessels of undetermined "nutritional" value to the growing tumor. Whereas Folkman (2) maintains that no evidence exists of "lymphangiogenesis factors," Liu et al in this issue of *Lymphology* (9) and others (reviewed in 5) are currently pinpointing "lymphangiogenic" and "lymphangiogenic"

factors” and standardizing lymphangiogenesis assays *in vivo* and *in vitro*. It remains to compare these lymphatic growth promoting and inhibiting factors with the extensive literature on “hemangiogenic factors” in standardized “hemangiogenesis assays.” Accordingly, until these answers are in, the question should remain open as to what extent lymphangiogenesis occurs in tumors. In tumor biology, as Pullinger and Nobel Laureate Florey (10) suggested in 1937 regarding “reactions in injured tissues, ... the presence of lymphatic proliferation [*sic* lymphangiogenesis] may well be as important ... as that of blood vessels” [*sic* hemangiogenesis].

#### REFERENCES

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