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Comorbidity and Lymphatic Disease: The Lymphatic Continuum Re-Examined

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Abstract

It has now been ~20 years since the original Lymphatic Continuum conference was convened, and this continuum has transitioned from a compelling concept to a reality. The explosive growth in our comprehension of lymphatic genetics, development, and function has expanded and modified our traditional views regarding what is, and is not, lymphatic disease. Groundbreaking investigations over the past decade have now defined a large and growing list of pathological conditions in which morphological or function lymphatic alterations can be identified. This list includes atherosclerosis and dyslipidemia, hypertension and other cardiovascular diseases, inflammation and inflammatory bowel disease, obesity, narrow angle glaucoma, and, most recently and compellingly, neurodegenerative disease. The sometimes overlapping but largely disparate nature of these various aforementioned disease categories suggests that the presence, or absence, of structural or functional lymphatic derangements may represent a previously unrecognized unifying influence in the maintenance of health and the promotion of disease. Future investigation of lymphatic mechanisms in disease will likely continue to elucidate the influences of lymphatic dysfunction, perhaps subtle, that can invest other, seemingly unrelated, diseases. In future, such discoveries will provide mechanistic insights and may potentiate the development of a new lymphatic-based approach to human disease diagnosis and therapeutics.

Keywords: lymphatic disease, lymphatic system, comorbidity

The Lymphatic Continuum, a multidisciplinary symposium to highlight lymphatic biology and research, was convened in 2002 on the campus of the National Institutes of Health (NIH).[1] The intent of this conference was not only to highlight the new and emerging focus on the developmental and functional biology of the lymphatic system, but, very specifically, to stimulate investigation into the role of lymphatic biology and pathology across the so-called lymphatic continuum (Table 1), where a putative role for the vital immunocirculatory network could already be surmised in a variety of pathological contexts, including, but not limited to, cancer, wound healing, infection, fibrosis, autoimmune disease, vascular biology, and obesity and metabolic derangements, among many others.[1]

The years that immediately followed the Lymphatic Continuum conference at the NIH witnessed an explosive growth in the investigative field of lymphatic biology, prompting the organization of a second follow-up conference, entitled The Lymphatic Continuum Revisited.[2] With the interval development of more robust techniques for immunohistochemical imaging,[3] animal modeling of lymphatic disease,[4] peptide targeting of lymphatic vessels,[5] and other advances, it had become increasingly relevant to consider not only the spectrum of intrinsic diseases of the lymphatic system,[6] but also the role of lymphatic function and dysfunction in cancer[7] and metastasis,[8] obesity,[9] lung disease,[10] and in immune function in general.[11]

It has now been ~20 years since the original Lymphatic Continuum conference was convened, and this continuum has transitioned from a compelling concept to a reality. The explosive growth in our comprehension of lymphatic genetics, development, and function has expanded and modified our traditional views regarding what is, and is not, lymphatic disease. Groundbreaking investigations over the past decade have now defined a large and growing list of pathological conditions in which morphological or function lymphatic alterations can be identified. This list includes atherosclerosis[12] and dyslipidemia,[13,14] hypertension[15–17] and other cardiovascular

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Table 1. The Lymphatic Continuum

• Vasculature of cancer and cancer metastasis
• Autoimmune disease
• Chronic infection and inflammation
• Organ transplantation
• Coronary artery disease and CHF
• Obesity, metabolic syndrome, and DM
• CNS degenerative disease

CHF; CNS; DM.

diseases,[18–20] inflammation[21] and inflammatory bowel disease,[22,23] obesity,[24,25] narrow angle glaucoma,[26,27] and, most recently and compellingly, neurodegenerative disease.[28–31]

This most recently uncovered impact of the meningeal lymphatics in the pathogenesis of neurodegenerative disease is an emerging and rapidly expanding area of research. Experimental modeling in mice through meningeal lymphatic ablation demonstrates amyloid-β accumulation in the meninges, thus supporting the hypothesis that they contribute to the pathological impact of interstitial macromolecular accumulation that characterizes neurodegenerative pathologies such as Alzheimer's disease.[29,30] Similarly, the potential impact of altered lymphatic function upon the evolution of cardiac and vascular disease has long been hypothesized; this mechanistic inference is now supported by growing evidence that disturbed cardiac lymph clearance promotes cardiac edema[19] and, furthermore, that cardiac lymphangiogenesis is a participating event in the natural history of myocardial infarction.[18]

Of course, patients with an established lymphatic diagnosis should be carefully scrutinized for the presence of potential comorbid disease states. However, the implications of these findings are much more far reaching. The sometimes overlapping but largely disparate nature of these various aforementioned disease categories suggests that the presence, or absence, of structural or functional lymphatic derangements may represent a previously unrecognized unifying influence in the maintenance of health and the promotion of disease. The interrelated nature of the various forms of lymphatic pathology is underscored, in part, by the recent demonstration of a shared biomarker among patients with lymphatic vascular diseases, acquired lymphedema, and lipedema, respectively.[32]

Continued attempts to identify reliable biomarkers of lymphatic dysfunction will likely be valuable, not only in the future clinical assessment putative intrinsic lymphatic vascular pathologies, but, in addition, to elucidate the subtler manifestations of lymphatic dysfunction that can potentiate other, seemingly unrelated, diseases. In future, such discoveries will provide mechanistic insights and may potentiate the development of a new lymphatic-based approach to human disease diagnosis and therapeutics.

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