

Experimental Lymphedema: Can Cellular Therapies Augment the Therapeutic Potential for Lymphangiogenesis?

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The lymphatic system, the subject of centuries of paradoxical relative neglect, is finally and deservedly coming into focus.^{1,2} This integral component of the mammalian vasculature plays a central role in immunocompetence and fluid homeostasis and, therefore, is often an active participant in the progression of disease.^{3,4}

The biology of regional lymphatic vascular insufficiency is complex. When regional lymphatic flow is insufficient to maintain tissue fluid homeostasis, interstitial fluid accumulates and swelling ensues. Furthermore, in addition to this readily observed role in the maintenance of tissue fluid homeostasis, functioning lymphatics are crucial to the traffic of immunocompetent cells from the tissue periphery to the lymph node, where antigenic processing can occur.⁵

Lymphedema is the all-too-frequent clinical consequence of impaired lymphatic function. The condition does not typically threaten survival, yet the advent of lymphedema can significantly undermine productivity and quality of life for affected individuals. The sequelae of lymphedema include loss of function, restriction of movement, risk of infection, and profound alterations in psychosocial adjustment⁶ that include fear, affective disorders, and loss of self-esteem and body image.⁷ Lymphedema is a chronic debilitating disease for which there continues to be a great deal of clinical confusion and treatment delay.⁸

The current available treatments for lymphedema do not address the causal molecular pathophysiology and thus provide only modest delays in the progression to end-stage sequelae of lymphedema.⁹ In recent years, however, the

identification of the molecular components of the lymphatic developmental apparatus has made it feasible to contemplate the therapeutic administration of lymphatic-specific growth factors (therapeutic lymphangiogenesis) to alleviate the tissue consequences of lymphatic vascular insufficiency.^{10–15}

Despite initial perceptions of benefit, the enthusiasm for growth factor therapy has not been universal. The precise mechanism for vascular endothelial growth factor receptor 3–mediated amelioration of secondary lymphangiogenesis is unclear. There are currently contrasting observations that exogenous growth factor administration to sites of lymphatic injury augments early lymphatic endothelial cell proliferation but without the development of functionally competent vasculature.^{16–18} Furthermore, it seems that the ultimate ability of the lymphatic vasculature to regenerate after injury might be governed by an exquisite balance between prolymphangiogenic and antilymphangiogenic cytokines.¹⁹

In the current issue of the *Journal of the American Heart Association*, Shimizu et al²⁰ address this persistent quandary in experimental therapeutics with a modification of the prolymphangiogenic approach. Specifically, they administered adipose-derived regenerative cells to a murine tail model of acquired lymphedema to assess whether these cells might serve to augment meaningful lymphatic neovascularization. The findings of this investigation include the observation of a direct lymphangiogenic response to implantation of adipose-derived regenerative cells into the zone of lymphovascular deficiency. In addition, the researchers observe that these cells in culture produce vascular endothelial growth factor C, which is capable of augmenting lymphangiogenesis. Finally, they report that the in vivo administration of the cellular material resulted in augmented recruitment of bone marrow–derived M2 macrophages that could serve the role of lymphatic endothelial progenitor cells. These findings are certainly congruent with other recent observations.²¹

The functional significance of the authors' findings ultimately must be demonstrated through further investigation. First, it must be acknowledged that the animal models for lymphedema are imperfect.²² The authors used a frequently studied small rodent model of acquired lymphedema^{11–13,16–19} that offers a high-throughput means to readily observe histological, microvascular, and molecular events. However,

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the ability to translate therapeutic observations in this model to human pathology might be limited. Cytokine-stimulated therapeutic lymphangiogenesis, whether via direct ligand administration or, as used here, indirect cell-mediated augmentation, simply might be insufficient to foster the development of the competent lymphatic architecture that is needed to restore lymph flow. Nevertheless, continued investigation and the creative approaches described here certainly are warranted. Patients with lymphedema undoubtedly will one day be the beneficiaries of these focused investigations.

Disclosures

None.

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