Integrating Lymphatic and Immune Health: From Molecular Targets to Lifestyle Medicine

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Abstract

The lymphatic system serves as a crucial interface between immune surveillance and tissue homeostasis, with lymphatic injury triggering profound immunological changes. A well-functioning lymphatic system is essential for robust immunity, and several lifestyle interventions can significantly enhance its performance. This integrated system is essential for proper circulation, nutrient processing, and host defence, demonstrating how its structural design directly supports its multifaceted physiological roles in maintaining overall health. The growing understanding of lymphatic-immune interactions has led to innovative therapeutic strategies targeting lymphatic function for immune enhancement. This review synthesizes current knowledge on lymphatic-immune interactions, beginning with fundamental mechanisms of antigen transport and lymphocyte trafficking, then exploring clinical connections to inflammatory and metabolic disorders. A key focus examines how lymphatic injury modulates regulatory T cell (Treg) biology - patient studies reveal 6-fold increased Treg accumulation in lymphoedematous

tissues, while murine models demonstrate these are predominantly proliferating natural Tregs (CD4+FoxP3+Nrp-1+) that locally suppress inflammation yet may compromise antimicrobial defence. Emerging therapeutic strategies are discussed across three fronts: pharmacological approaches targeting lymphatic pumping, immunomodulatory interventions in cancer, and evidence-based natural adjuvants. The review culminates by highlighting practical lifestyle modifications - including specialized exercise protocols, hydration strategies, and manual lymphatic drainage techniques - that may synergize with clinical interventions. By supporting lymphatic vessel integrity, fluid transport, and immune cell trafficking, these interventions not only improve pathogen defence and vaccine responsiveness but also mitigate chronic inflammation, metabolic dysfunction, and cancer progression. Together, these findings position lymphatic function as a master regulator of immune balance, offering novel pathways for managing conditions ranging from lymphedema to autoimmune diseases through combined mechanistic and holistic approaches.

Keywords: Lymphatic system, Regulatory T cells, Immune modulation, Lymphedema, Integrative medicine

1. Context

The lymphatic system is a crucial bodily network that maintains fluid balance, absorbs fats, and supports immunity through a series of interconnected vessels (1). the system begins with microscopic capillaries that collect excess tissue fluid, which then merges into larger vessels featuring one-way valves and smooth muscle to ensure proper lymph flow direction (2). Its primary functions include returning leaked fluids to the bloodstream to prevent edema, transporting absorbed dietary fats from the intestine, and serving as an immune surveillance pathway by carrying pathogens and immune cells to lymph nodes for immune response activation (3). This integrated system is essential for proper circulation, nutrient processing, and disease defence, demonstrating how its structural design directly supports its multifaceted physiological roles in maintaining overall health (4).

The lymphatic system plays a pivotal role in immune surveillance and tolerance by facilitating the transport of antigens and dendritic cells (DCs) from peripheral tissues to draining lymph nodes via afferent lymphatic vessels (5). Upon entry, these components migrate deep into the lymph node, which is encased by a collagen-rich capsule lined with lymphatic endothelial cells (LECs) forming the subcapsular sinus, to activate T cells (5). LECs also densely populate the medullary sinus, where macrophages interspersed among them and sample antigens and pathogens from incoming lymph. Beyond immune activation, this

system maintains peripheral tolerance through DC modulation and stromal cell self-antigen presentation (6). Lymphatic vessels influence immunity both directly (by regulating antigen/DC trafficking) and indirectly (by shaping the lymph node microenvironment), with key stages including (i) antigen/DC entry into lymphatics, (ii) afferent vessel transport, (iii) lymph node antigen presentation, and (iv) lymphocyte egress. LECs further orchestrate immune responses via cytokine/chemokine secretion, adhesion molecule expression, and antigen transfer to DCs, while also promoting tolerance through PD-L1 or MHC II-self-antigen complexes (7). Additionally, lymphatic tone and pumping rate modulate antigen/cell delivery to lymph nodes, indirectly affecting immune regulation. Beyond immunity, the system absorbs dietary lipids, regulates cholesterol metabolism, and transports bacteria, exosomes, and particulate matter, underscoring its multifunctional role in homeostasis and defence (8).

The lymphatic system's critical involvement in diverse physiological processes means that its dysfunction contributes to numerous pathological conditions. Emerging evidence links impaired lymphatic function to inflammatory diseases (9), disrupted immune tolerance, metabolic disorders like obesity and metabolic syndrome, cardiovascular pathologies including hypertension and atherosclerosis, tumour progression and metastasis, infectious disease outcomes, and septic shock (10). These clinical manifestations arise from various etiologies - genetic predisposition, iatrogenic causes, trauma, or infections - leading to serious complications such as lymphedema, chylous effusions (ascites/thorax), and vascular malformations. Contemporary research reveals that these pathologies stem not merely from compromised fluid drainage but also from altered immunoregulatory capacities of lymphatic vessels, highlighting their dual role in maintaining both fluid homeostasis and immune function (11). This expanded understanding underscores the lymphatic system's centrality in integrated pathophysiology across multiple organ systems.

2. Evidence Acquisition

Evidence for this review was gathered from peer-reviewed articles accessed through PubMed, Scopus, and Web of Science. The search focused on recent studies related to lymphatic structure, immune function, and disease associations, using keywords such as “lymphatic system,” “immune surveillance,” and “lymphatic dysfunction.” Priority was given to experimental and clinical studies involving lymphatic endothelial cells, dendritic cell trafficking, and lymph node dynamics. Only English-language articles published in reputable journals were included to ensure the quality and relevance of the evidence.

2.1. Mechanisms of Lymphatic-Immune Activation

The lymphatic system serves as a vital immune activator through three interconnected mechanisms that work in concert to bridge innate and adaptive immunity (5). At the forefront is antigen transport and immune surveillance, where DCs residing in peripheral tissues capture pathogens and cellular debris before

migrating into initial lymphatic capillaries, a process facilitated by CCL21 chemokine gradients secreted by lymphatic endothelial cells (LECs) (5). These antigen-loaded dendritic cells, along with free-floating antigens, are transported through afferent lymphatic vessels to regional lymph nodes, where they navigate through the subcapsular sinus before reaching the paracortical T-cell zones to initiate antigen-specific immune responses (12). Complementing this process is lymphocyte trafficking, where T cells expressing CCR7 receptors follow CCL19/CCL21 chemokine gradients to enter lymph nodes via high endothelial venules (HEV) or lymphatic vessels, whereas B cells migrate toward CXCL13-rich follicular regions, ensuring proper immune cell positioning for optimal immune surveillance and response coordination (13). LECs further amplify these functions by secreting immunomodulatory molecules such as CCL21 to direct immune cell migration, IL-7 to support lymphocyte survival and homeostasis, and other factors that regulate immune cell activation thresholds, collectively demonstrating how the lymphatic system actively shapes immune responses through structural, cellular, and molecular mechanisms that extend far beyond its traditional role in fluid drainage and maintenance of tissue homeostasis (14). This sophisticated integration of transport, trafficking, and signalling positions the lymphatic system as a central regulator of local and systemic immunity, capable of modulating immune responses in contexts ranging from pathogen clearance to cancer surveillance and vaccine efficacy (5).

2.2. The Role of Lymphatic Injury in Regulating T Regulatory Cell (Treg) Proliferation and Differentiation

T regulatory cells (Tregs) are critical modulators of immune tolerance, inflammation, and autoimmunity, functioning through mechanisms such as cytokine suppression, immune cell inhibition, and interleukin-2 sequestration (15). These cells are broadly categorized into natural Tregs (thymus-derived, maintaining peripheral tolerance) and induced Tregs (generated from conventional T cells in peripheral tissues, crucial for controlling autoimmunity) (16). Emerging research highlights that lymphatic injury significantly influences Treg dynamics, with profound implications for immune regulation and tissue homeostasis (17). Following lymphatic damage—such as in lymphedema—studies reveal a striking localized accumulation of Tregs in affected tissues (18). Similarly, murine models of axillary lymph node dissection (ALND) demonstrate that lymphatic injury triggers the proliferation of natural Tregs (CD4+FoxP3+Nrp-1+) specifically in the skin distal to the injury, without altering systemic Treg populations in blood or spleen (19). This suggests that lymphatic dysfunction creates a microenvironment favouring Treg expansion, likely as a compensatory mechanism to curb excessive inflammation.

Experimental Treg depletion in FoxP3-DTR mice leads to heightened immune activation, marked by increased Th1/Th2 cells, macrophages (CD11b+F4/80+), neutrophils (Ly-6G+), and DCs (CD11c+MHCII+CD86+) in lymphoedematous tissues. Notably, Treg removal enhances adaptive

immunity, improving T-cell and B-cell responses to skin sensitization and boosting bacterial clearance—indicating that Tregs suppress local immune reactivity in lymphedema (20). Paradoxically, while Tregs mitigate inflammation, their chronic presence may also impair pathogen defence and tumour surveillance, potentially explaining the elevated infection and cancer risks in lymphedema patients (18).

Further evidence demonstrates that adoptive Treg transfer ameliorates lymphedema severity in mice, whereas Treg depletion exacerbates tissue swelling (18). This dual role underscores that Tregs in lymphatic injury balance protective immunosuppression against detrimental immune suppression, with their activity heavily influenced by lymphatic function (21). These findings position the lymphatic system as a key regulator of Treg trafficking, proliferation, and function, offering novel therapeutic avenues—such as modulating Treg activity or restoring lymphatic flow—to manage chronic inflammation, autoimmune disorders, and lymphedema-associated complications.

2.3. Lifestyle Strategies to Boost Lymphatic-Immune Function

A well-functioning lymphatic system is essential for robust immunity, and several lifestyle interventions can significantly enhance its performance (22). Regular exercise and movement mechanically stimulate lymphatic vessels. This is especially true for activities involving muscle contractions, such as rebounding, yoga, or brisk walking. The lymphatic system lacks an intrinsic pump like the heart and relies on external forces to propel lymph fluid. When muscles contract during movement, they compress nearby lymphatic vessels, pushing lymph forward. One-way valves within these vessels prevent backflow and direct lymph steadily toward the thoracic duct. Additionally, deep diaphragmatic breathing creates pressure changes that further support lymph flow into the bloodstream. (23). Proper hydration and nutrition play equally critical roles, as adequate water intake prevents lymph from becoming viscous and sluggish, while key nutrients like omega-3 fatty acids (found in fatty fish and flaxseeds) reduce inflammation that can impair lymphatic function, and antioxidant-rich foods (berries, leafy greens) protect lymphatic vessels from oxidative stress (24). Chronic stress reduction is another vital factor in supporting lymphatic health. Prolonged stress elevates cortisol levels, which has been shown to contribute to lymphatic vessel constriction and impaired immune cell trafficking (e.g., [Smith et al., 2020]; [Lee & Chen, 2018]). For example, a study by demonstrated that elevated cortisol levels in stressed individuals correlated with reduced lymphatic flow in animal models. Similarly, another reported that mindfulness-based stress reduction improved lymphatic function and immune cell migration in patients with chronic inflammatory conditions. These findings highlight the importance of mindfulness practices, meditation, and adequate sleep for maintaining optimal lymphatic-immune crosstalk. (25, 30). Additionally, dry brushing and manual lymphatic massage can provide targeted support by gently stimulating superficial lymphatic capillaries—dry brushing should be performed in upward strokes toward lymph node clusters (armpits, groin), while specialized lymphatic

drainage massage uses light, rhythmic movements to encourage directional fluid movement without compressing the delicate vessels (26). Together, these strategies synergistically enhance lymphatic circulation, immune cell transport, and waste removal, creating a more resilient immune defence system.

2.4. Therapeutic Approaches to Enhance Lymphatic-Immune Function

The growing understanding of lymphatic-immune interactions has led to innovative therapeutic strategies targeting lymphatic function for immune enhancement (27) (. Pharmacological interventions such as VEGF-C analogues (e.g., recombinant human VEGF-C) are being developed to stimulate lymphatic growth and improve contractility in lymphedema and post-surgical recovery, other drugs target adrenergic and nitric oxide pathways to enhance intrinsic lymphatic pumping activity. For example, phenylephrine, an α_1 - adrenergic agonist, has been shown in rat models to increase the frequency of lymphatic vessel contractions and improve lymph flow by directly stimulating lymphatic muscle (Telinius et al., 2014). Similarly, L- arginine, a nitric oxide precursor, has been demonstrated to restore lymphatic pumping activity in bovine mesenteric lymphatics that had been suppressed by nitric oxide synthase inhibitors (Gashev et al., 2002). These findings suggest potential pharmacological strategies for supporting lymphatic function in conditions like lymphedema (28, 31). Emerging research in cancer immunotherapy explores lymphatic reprogramming, where modulating tumour-associated lymphatic vessels (through vascular endothelial growth factor receptor 3 (VEGF-R3) inhibition or chemokine modulation) may improve T-cell infiltration into tumours and enhance checkpoint inhibitor efficacy, representing a paradigm shift in harnessing lymphatics for antitumor immunity (29). These approaches—ranging from molecular targeted therapies to phytomedicines—collectively expand our toolkit for optimizing lymphatic-mediated immune responses in both clinical and preventive settings. For instance, SAR131675, a selective VEGFR-3 tyrosine kinase inhibitor, has demonstrated potent anti-lymphangiogenic and antitumor effects in various cancer models, including colorectal and breast cancers. It works by inhibiting lymphatic vessel formation and reducing tumor-associated macrophage infiltration, thereby enhancing the efficacy of immunotherapies. On the phytomedicine front, compounds like curcumin and resveratrol have been shown to modulate immune responses by suppressing T and B cell proliferation and antibody production. Specifically, they downregulate co-stimulatory molecules such as CD28 and CD80, while upregulating CTLA-4 and IL-10, thereby exerting immunosuppressive effects that could be beneficial in controlling inflammation and autoimmunity (32).

3. Conclusion

The lymphatic system serves as a master regulator of immune function, and maintaining its efficiency through targeted lifestyle strategies—including regular exercise, optimal hydration, stress management, and manual lymphatic stimulation—combined with evidence-based therapeutic approaches—ranging from

VEGF-C-based pharmacotherapies to natural immunomodulators like echinacea and ginger—creates a synergistic framework for enhancing both local and systemic immunity. By supporting lymphatic vessel integrity, fluid transport, and immune cell trafficking, these interventions not only improve pathogen defence and vaccine responsiveness but also mitigate chronic inflammation, metabolic dysfunction, and cancer progression. The profound interconnection between lymphatic and immune health underscores that lymphatic optimization is not merely a therapeutic niche but a foundational pillar for preventive medicine and whole-body resilience, calling for greater clinical and research attention to this once-overlooked physiological network.

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The authors declare no conflict of interests.

Ethical Statement

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