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Beyond Angiogenesis: Lymphangiogenesis as an Emerging Frontier in Periodontal Regeneration

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Abstract
Periodontal regeneration requires coordinated restoration of the cementum, periodontal ligament and alveolar bone within a biologically controlled healing environment. Although angiogenesis has traditionally received considerable attention because of its role in supplying oxygen, nutrients and circulating cells to regenerating tissues, the contribution of the lymphatic vasculature has received comparatively little investigation. Increasing evidence indicates that lymphatic vessels participate actively in interstitial fluid regulation, immune-cell trafficking, inflammatory resolution and tissue remodelling. These functions may be particularly relevant to periodontal disease, in which persistent inflammation and impaired tissue homeostasis contribute to progressive destruction of the supporting tissues.

Experimental studies have demonstrated that gingival lymphatic drainage can influence inflammatory responses and protect against inflammation-associated alveolar bone loss. Alterations in lymphatic architecture and function have also been observed during periodontal inflammation and oral wound healing. More recent evidence suggests that lymphatic remodelling is spatially coordinated during periodontal repair and that stimulation of the vascular endothelial growth factor-C (VEGF-C)/vascular endothelial growth factor receptor-3 (VEGFR-3) pathway may improve lymphatic function and support alveolar bone repair. Findings from skeletal regeneration models further indicate that lymphatic endothelial cells can influence bone healing through paracrine signalling mechanisms.

This review summarizes the biological role of periodontal lymphatics, their relationship with periodontal inflammation, and emerging evidence linking lymphatic function with oral and skeletal regeneration. It also discusses the therapeutic potential of controlled lymphangiogenesis, including localized VEGF-C delivery and biomaterial-based approaches.

Keywords: *lymphangiogenesis; periodontal regeneration; lymphatic vessels; VEGF-C; VEGFR-3; periodontitis; alveolar bone regeneration; oral wound healing*

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I. Introduction

Periodontitis is a chronic inflammatory disease in which a dysbiotic microbial challenge interacts with an inappropriate or unresolved host response, resulting in destruction of the periodontal connective tissues and alveolar bone. Successful periodontal treatment therefore extends beyond microbial control and requires restoration of a biological environment capable of supporting inflammation resolution, tissue repair and, where possible, true regeneration. [1]

Periodontal regeneration differs fundamentally from repair. True regeneration involves the coordinated formation of new cementum, periodontal ligament and alveolar bone and the restoration of their anatomical and functional relationships. Current regenerative approaches include guided tissue regeneration, bone grafting, enamel matrix derivatives, growth-factor-based therapies and platelet concentrates, as well as increasingly sophisticated tissue-engineering strategies. Despite these advances, clinical outcomes remain variable and are influenced by defect morphology, local and systemic biological conditions, wound stability and the complexity of periodontal healing. [2], [3]

Vascular remodelling is an essential component of tissue repair. Consequently, periodontal regenerative research has historically focused predominantly on angiogenesis, which provides oxygen, nutrients and circulating cellular components to healing tissues. In contrast, the lymphatic vasculature has received considerably less attention. The lymphatic system was traditionally regarded primarily as a drainage network, but it is now

recognized as an active regulator of tissue-fluid homeostasis, immune surveillance, inflammatory responses and tissue remodelling. [4], [5]

Despite increasing recognition of the biological importance of lymphatic vessels, their contribution to periodontal regeneration remains insufficiently understood. Given their roles in interstitial-fluid homeostasis, immune-cell trafficking and inflammatory regulation, lymphatic remodelling may represent an important component of the periodontal regenerative microenvironment. [4], [5] This review summarizes the current understanding of periodontal lymphatic biology and examines the relationship between lymphangiogenesis, periodontal inflammation and tissue repair. It further discusses emerging evidence linking lymphatic function with oral and skeletal regeneration and evaluates the therapeutic potential of controlled lymphangiogenesis, including localized VEGF-C delivery and biomaterial-based strategies.

Lymphatic architecture of the periodontium

The lymphatic system consists of initial lymphatic capillaries, collecting lymphatic vessels, lymph nodes and larger lymphatic trunks. Initial lymphatics are thin-walled, blind-ended vessels specialized for uptake of interstitial fluid, proteins, inflammatory mediators, cellular debris and immune cells. Lymph is subsequently transported through collecting vessels towards regional lymph nodes and ultimately into the systemic circulation. [4], [5]

Within the gingiva and periodontal tissues, lymphatic drainage is particularly relevant because these tissues are continuously exposed to microbial products and mechanical challenges. Efficient lymphatic function contributes to maintenance of interstitial-fluid homeostasis and supports local immune surveillance. [4], [5] Evidence that lymphangiogenic mediators are expressed in human gingival tissues provides a biological basis for investigating lymphatic signalling in periodontal disease and regeneration .[6–9]

The VEGF-C/VEGF-D signalling axis and its receptor VEGFR-3 represent major regulators of lymphatic endothelial-cell development and function. Activation of VEGF-C/VEGFR-3 signalling promotes lymphatic endothelial-cell proliferation, migration and survival and contributes to lymphatic remodelling. [10], [15]

Lymphangiogenesis and its biological significance

Lymphangiogenesis refers to the formation and remodelling of lymphatic vessels from pre-existing lymphatic structures. Although it was historically viewed primarily as a mechanism for restoring fluid drainage, current evidence indicates that lymphatic endothelial cells have broader biological functions. [4],[15]

Lymphatic endothelial cells participate in immune-cell trafficking, inflammatory regulation and extracellular-matrix remodelling. Emerging evidence also indicates that lymphatic vessels can influence cell proliferation, stem-cell niches and tissue regeneration through paracrine mechanisms. [16]

This broader biological role is particularly relevant to periodontal regeneration. The outcome of periodontal healing depends not only on the recruitment and differentiation of osteogenic and periodontal ligament cells but also on the timely resolution of inflammation and restoration of tissue homeostasis. Lymphatic remodelling may therefore represent an additional component of the regenerative microenvironment. [16]

The VEGF-C/VEGFR-3 signalling pathway

VEGF-C and VEGF-D are important regulators of lymphatic endothelial biology. Their interaction with VEGFR-3 activates signalling pathways involved in lymphatic endothelial-cell proliferation, migration and survival. [14],[15]

A simplified biological sequence can be proposed:

Tissue injury or inflammation → VEGF-C production → VEGFR-3 activation → lymphatic endothelial-cell survival, proliferation and migration → lymphatic remodelling → improved lymphatic function and immune regulation.

Studies in gingival tissues have demonstrated expression of lymphangiogenic mediators, while inflammatory stimulation of gingival fibroblasts can increase VEGF-C expression. [8] These observations provide a mechanistic link between periodontal inflammation and lymphatic remodelling.

Importantly, the biological consequences of VEGF-C stimulation may depend on the magnitude, timing, location and duration of signalling. Therapeutic strategies should therefore aim to restore functional lymphatic networks rather than simply increase lymphatic vessel density. [11], [17]

Lymphatic remodelling during periodontal inflammation

Periodontal inflammation is accompanied by changes in the lymphatic vasculature. Early experimental observations suggested that gingival lymphatics may contribute to protection against periodontal inflammation by facilitating the removal of excess interstitial fluid and inflammatory products and by supporting immune-cell trafficking. [6]

Mkonyi and colleagues demonstrated that gingival lymphatic drainage protects against *Porphyromonas gingivalis*-induced alveolar bone loss in mice. [6] This finding provided important experimental evidence that

lymphatic function can influence periodontal tissue destruction rather than merely accompany the inflammatory response.

Subsequent work further supported a relationship between periodontal inflammation and lymphatic structural changes. Gingival lymphatic hyperplasia has been observed in inflammatory conditions, indicating that the lymphatic network responds dynamically to the local inflammatory environment. [7], [8]

However, lymphatic vessel number and lymphatic function should not be considered equivalent. An increase in vessel density does not necessarily indicate effective lymph transport. Functional characteristics such as vessel organization, flow and drainage capacity may be more important determinants of biological outcome. [7], [9]

Lymphatic dysfunction and alveolar bone loss

Experimental periodontitis models provide evidence that altered lymphatic function may contribute to alveolar bone destruction. Wang and colleagues reported increased lymphatic capillaries together with changes in collecting lymphatics, delayed lymphatic flow and enhanced osteoclast-associated alveolar bone loss in experimental periodontitis. VEGF-C treatment improved lymphatic function and reduced inflammation-associated alveolar bone loss. [9]

These observations support a potential relationship between periodontal inflammation and lymphatic dysfunction:

Periodontal inflammation → abnormal lymphatic remodelling → impaired lymphatic transport → persistence of the inflammatory environment → enhanced osteoclast activity → alveolar bone loss.

This sequence should be regarded as a proposed biological model rather than an established causal pathway in humans. Nevertheless, it provides a rationale for investigating lymphatic function as a potential regulator of the balance between periodontal destruction and repair. [9]

Lymphatic vessels in oral wound healing

The relevance of lymphatic function extends beyond established periodontal disease to the wound-healing process itself. Periodontal regenerative procedures inevitably create a wound environment in which inflammation, vascular remodelling, extracellular-matrix deposition and tissue maturation occur sequentially.

Experimental studies examining tooth-extraction wounds have provided direct evidence that initial lymphatics contribute to oral wound healing. Virtej and colleagues demonstrated that mice lacking initial mucosal lymphatics exhibited delayed epithelialization and alveolar bone healing, accompanied by persistent inflammation and reduced EGF levels. Interestingly, experimentally induced lymphatic hyperplasia did not accelerate healing, further emphasizing that functional lymphatic organization may be more important than vessel density alone. [18]

These observations are relevant to periodontal regenerative surgery because successful regeneration requires transition from an inflammatory environment to a proliferative and remodelling phase. Adequate lymphatic function may facilitate this transition through interstitial-fluid clearance and immune-cell trafficking. [18]

Importantly, the findings also suggest that the timing of lymphatic involvement may be critical. Lymphatic vessels may have distinct functions during the early inflammatory phase compared with later stages of tissue remodelling. Therefore, future regenerative strategies should consider not only whether lymphangiogenesis occurs, but also when and where it occurs. [18]

Lymphangiogenesis and bone regeneration

Evidence from skeletal tissues provides additional support for a relationship between lymphatics and bone regeneration. Hominick and colleagues demonstrated that VEGF-C promotes lymphatic development within bone and showed an association between lymphatic biology and bone homeostasis. [10]

More recently, Biswas and colleagues reported that lymphatic vessels contribute to bone regeneration following injury and identified lymphatic endothelial-cell-derived CXCL12 as an important regenerative signal. [19] These findings suggest that lymphatic endothelial cells may influence skeletal repair through mechanisms extending beyond fluid drainage.

Although findings from long bones and other skeletal tissues cannot be directly extrapolated to periodontal defects, they provide an important biological framework for investigating lymphatic–bone interactions within the alveolar environment. [10], [19]

The periodontal tissues present a particularly complex regenerative setting because alveolar bone is closely integrated with the periodontal ligament and cementum. Future studies should therefore determine whether lymphatic endothelial cells communicate directly with periodontal ligament cells, osteoblasts, mesenchymal progenitor cells and immune-cell populations during periodontal regeneration.

Lymphatic regulation of inflammation resolution

Persistent inflammation is one of the major biological barriers to predictable periodontal regeneration. Resolution of inflammation requires removal or neutralization of inflammatory mediators, appropriate trafficking of immune cells and restoration of tissue homeostasis.

Lymphatic vessels can contribute to these processes through interstitial-fluid drainage and immune-cell transport. Consequently, lymphatic remodelling may influence the transition from inflammation to proliferation and subsequent tissue maturation. [4], [5], [16]

This concept is particularly relevant to periodontitis, in which unresolved inflammation promotes connective-tissue destruction and osteoclast-mediated bone resorption. Rather than viewing lymphangiogenesis as an isolated vascular event, it may be more appropriate to consider it as one component of a broader inflammatory-resolution network.

Angiogenesis and lymphangiogenesis

Angiogenesis and lymphangiogenesis should not be considered competing biological processes. Rather, they may represent complementary components of tissue regeneration.

Angiogenesis contributes to oxygen and nutrient delivery and supports formation of vascularized granulation tissue. Lymphangiogenesis, in contrast, contributes to fluid drainage, immune-cell trafficking, inflammatory regulation and tissue homeostasis. [4], [5], [20]

A coordinated vascular model of periodontal regeneration can therefore be proposed:

Angiogenesis + lymphangiogenesis + inflammation resolution → functional regenerative microenvironment → tissue repair and regeneration.

This integrated model may help explain why simply increasing vascularization is unlikely to be sufficient for predictable periodontal regeneration. Successful healing requires coordinated regulation of blood vessels, lymphatic vessels, immune responses and regenerative cell populations. [20]

Therapeutic lymphangiogenesis

Therapeutic lymphangiogenesis refers to deliberate stimulation or restoration of functional lymphatic networks to improve tissue repair. VEGF-C is an attractive candidate because of its established role in lymphatic endothelial-cell activation through VEGFR-3. [14], [17]

Experimental work using engineered fibrin-binding VEGF-C has demonstrated that localized lymphangiogenic stimulation can promote lymphatic remodelling, immune-cell trafficking and matrix remodelling during wound healing. [12] These findings have potential relevance to periodontal regeneration because periodontal membranes, hydrogels and other biomaterials can potentially serve as local delivery platforms. [13], [21]

However, therapeutic lymphangiogenesis should not be equated with indiscriminate stimulation of lymphatic vessel growth. An increase in vessel number without restoration of appropriate organization or function may not produce a regenerative benefit. Future interventions should therefore focus on controlled, spatially restricted and temporally appropriate lymphatic stimulation. [11], [12]

Lymphatic endothelial cells as therapeutic targets

The ability to study lymphatic endothelial cells derived directly from gingival tissue represents an important development in periodontal lymphatic research. Matsumoto and colleagues recently established primary gingiva-derived lymphatic endothelial cells and investigated their response to VEGF-C stimulation. Their findings demonstrated distinct molecular characteristics of gingival lymphatic endothelial cells and suggested that VEGF-C signalling promotes lymphatic endothelial-cell survival. [21-22]

Such cell-based models may allow investigation of interactions between lymphatic endothelial cells and other periodontal cell populations, including fibroblasts, periodontal ligament cells, immune cells and osteogenic progenitors.

These models may also help identify signalling pathways that could be targeted without relying exclusively on exogenous growth-factor administration. [23]

Emerging evidence for VEGF-C-mediated periodontal repair

Recent experimental evidence provides the most direct indication to date that lymphatic remodelling may contribute to periodontal repair. Matsumoto and colleagues investigated lymphatic changes during periodontal healing in a murine ligature-induced periodontitis model using tissue-clearing and light-sheet microscopy. [23]

Their observations indicated that lymphatic branching and density increased within the marginal gingiva during the granulation-tissue phase, while epithelial VEGF-C expression increased during repair. Local administration of VEGF-C C156S, a VEGFR-3-selective agonist, enhanced lymphatic function and was associated with improved alveolar bone repair. [23]

These findings are important because they move the field beyond descriptive identification of periodontal lymphatics towards experimental manipulation of lymphatic function. Nevertheless, the study remains preclinical, and the extent to which these findings translate to human periodontal defects remains unknown. [23]

A proposed model of lymphangiogenesis-mediated regeneration

Based on current evidence, a conceptual model for lymphatic involvement in periodontal regeneration can be proposed:

Periodontal regenerative intervention → tissue injury → inflammatory response → VEGF-C induction → VEGFR-3 activation → lymphatic endothelial-cell survival and proliferation → functional lymphatic remodelling → improved fluid drainage and immune regulation → inflammatory resolution → favourable regenerative microenvironment → osteogenic and periodontal-cell activity → periodontal tissue repair.

This model remains hypothetical and requires validation through mechanistic experiments. In particular, future studies should determine whether lymphatic stimulation directly enhances periodontal regeneration or whether its principal effect is mediated indirectly through modulation of inflammation and tissue homeostasis.

Lymphangiocrine signalling

Lymphatic endothelial cells may influence surrounding tissues through the secretion of soluble mediators, a process increasingly described in terms of lymphangiocrine signalling. CXCL12 is one example of a factor implicated in lymphatic regulation of bone regeneration. [19]

The concept of lymphangiocrine signalling raises several important questions in periodontal biology. Lymphatic endothelial cells may potentially influence periodontal progenitor cells, osteoblasts or other stromal populations through secreted factors in addition to their established role in fluid transport. [16], [19]

Characterizing these interactions could reveal regenerative pathways that are independent of direct VEGF-C administration and may ultimately provide more selective therapeutic targets.

Integration with periodontal regenerative therapies

Lymphatic modulation could potentially be incorporated into existing periodontal regenerative strategies rather than replacing established approaches.

In guided tissue regeneration, barrier membranes could potentially be engineered to provide controlled lymphangiogenic stimulation. In bone grafting procedures, lymphatic modulation could be combined with graft materials to influence the inflammatory environment surrounding the regenerating defect. Tissue-engineering approaches could integrate mechanical support, osteoconductive signals, angiogenic stimulation and lymphangiogenic cues within a single regenerative platform. [13], [22]

A future periodontal regenerative construct may therefore need to address several biological requirements simultaneously:

structural stability + angiogenesis + lymphangiogenesis + immunomodulation + osteogenesis + periodontal ligament regeneration.

Such an approach would more closely reflect the biological complexity of periodontal wound healing.

Potential relevance to peri-implant disease

Peri-implantitis is characterized by a dysbiotic microbial environment, chronic inflammation, soft-tissue destruction and progressive peri-implant bone loss. Given the potential role of lymphatic function in inflammatory regulation and bone remodelling, lymphatic modulation may eventually have relevance to peri-implant tissue repair.

At present, however, direct evidence supporting therapeutic lymphangiogenesis as a treatment for peri-implantitis is insufficient. This application should therefore be regarded as a hypothesis for future investigation rather than an established therapeutic strategy.

Limitations of current evidence

The current evidence base has several important limitations. First, much of the available research is derived from animal models or experimental systems. Second, the relationship between lymphatic vessel density and functional lymphatic transport remains incompletely characterized. Third, the optimal dose, route, timing and duration of VEGF-C stimulation have not been established. [7], [9], [11]

The biological effects of growth-factor-mediated lymphangiogenesis may also depend strongly on the local tissue environment. Excessive or poorly controlled growth-factor activity could produce undesirable vascular remodelling or alter inflammatory responses. [11]

Furthermore, periodontal regeneration is a multifactorial process. Improvements in lymphatic function alone may not be sufficient to restore the complex architecture of the periodontium. Future studies should therefore investigate lymphatic modulation within integrated regenerative models rather than as an isolated intervention.

II. Conclusion

Periodontal lymphatic biology is an emerging but underexplored component of periodontal regeneration. Evidence indicates that lymphatic vessels contribute to fluid homeostasis, immune-cell trafficking, inflammation regulation and tissue repair. Importantly, lymphatic vessel density alone may not indicate functional lymphatic competence; effective drainage and coordinated remodelling appear more relevant to tissue healing.

Recent evidence suggests that VEGF-C/VEGFR-3-mediated lymphatic stimulation may enhance lymphatic function and alveolar bone repair. However, current findings remain predominantly preclinical, and the mechanisms linking lymphatic remodelling with complete periodontal regeneration are not yet fully understood.

Future research should focus on functional lymphatic remodelling, lymphatic–immune interactions, lymphangiocrine signalling and lymphatic–periodontal cell communication. Integrating controlled lymphatic modulation with existing regenerative therapies may provide a more comprehensive approach to periodontal tissue engineering. Nevertheless, further mechanistic, safety and translational studies are required before therapeutic lymphangiogenesis can be considered for clinical application.

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