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Lymphaticosclerosis: a new way of thinking about lymphatic vessel obstruction

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Lymphoedema is a progressive condition that often manifests following cancer surgeries that involve removal or irradiation of lymph nodes. The symptoms may range from mild to severe and debilitating, and in the latter case can significantly increase susceptibility to infection and restrict quality of life.^{1,2} It is clear that removal of lymph nodes or severing of lymphatic vessels can cause an immediate interruption of the normal flow of lymph from the upstream vessel network into the downstream collecting vessels.³ However, the pathological mechanisms that progressively lead to severe secondary (acquired) lymphoedema are unclear, as are the reasons why different individuals receiving the same procedure may exhibit wide-ranging severities of lymphatic dysfunction.

In this issue of the *BJD*, Ogata *et al.* have investigated the change in phenotype of lymphatic smooth muscle cells during lymphoedema.⁴ The authors studied lymphatic vessels from 29 randomly chosen patients who had developed secondary leg lymphoedema after surgical removal of tumours, were refractory to congenital conservative therapy and received a lymphaticovenous anastomosis procedure. Typically, the collecting lymphatics that are responsible for pumping of lymph in the limbs have a thin layer of circular smooth muscle cells, which intrinsically contracts. The phasic contractions of these cells, in concert with intraluminal one-way valves composed of endothelial cells and connective tissue, allow forward propulsion of lymph through the system.⁵ Ogata *et al.* observed a striking change in the collecting lymphatic wall in patients with chronic lymphoedema,⁴ with a markedly thickened smooth muscle layer, increased collagen deposition and apparent invasion of smooth muscle cells into the intimal layer. In cases of more severe lymphoedema, stenosis or ‘lymphaticosclerosis’ of the lymphatic lumen due to overgrowth of lymphatic smooth muscle cells was apparent. In addition, labelling of the myosin heavy chain isoforms SM1 and SM2 was reduced in lymphatic smooth muscle, and transmission electron microscopy revealed an increase in synthetic organelles, such as sarcoplasmic reticulum and Golgi complex, while contractile myofilaments were reduced.⁴ Collectively, these findings suggest that the progression of surgery-induced lymphatic injury into lymphoedema involves re-entry of lymphatic smooth muscle cells into a proliferative stage to respond to the injury, followed by their failure to mature and remodel appropriately. This change in the phenotype

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of lymphatic smooth muscle is akin to a common problem with angioplasty: restenosis of the lumen after plaque removal due to the synthetic vascular smooth muscle phenotype.⁶

Several studies in recent years have identified various gene mutations that contribute either to primary (inherited) lymphoedema or facilitate the development of secondary lymphoedema. Most of these identified mutations affect the lymphatic endothelium and intraluminal valve structure.^{7–9} The current finding of altered lymphatic smooth muscle phenotypes associated with secondary lymphoedema prompts the hypothesis that gene mutations that affect lymphatic smooth muscle, particularly those that control the contractile vs. synthetic phenotype, may also contribute to lymphoedema progression. These new findings may provide an explanation for the wide variability in severity of lymphoedema in patients who undergo lymph node removal.

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References

1. Rockson SG. The unique biology of lymphatic edema. *Lymphat Res Biol.* 2009; 7:97–100. [PubMed: 19522679]
2. Rockson SG. Current concepts and future directions in the diagnosis and management of lymphatic vascular disease. *Vasc Med.* 2010; 15:223–31. [PubMed: 20483987]
3. Baker A, Semple JL, Moore S, et al. Lymphatic function is impaired following irradiation of a single lymph node. *Lymphat Res Biol.* 2014; 12:76–88. [PubMed: 24838016]
4. Ogata F, Fujii K, Koshim I, et al. Phenotypic modulation of smooth muscle cells in lymphedema. *Br J Dermatol.* 2015
5. Breslin JW. Mechanical forces and lymphatic transport. *Microvasc Res.* 2014; 96:46–54. [PubMed: 25107458]
6. Bennett MR. In-stent stenosis: pathology and implications for the development of drug eluting stents. *Heart.* 2003; 89:218–24. [PubMed: 12527687]
7. Ferrell RE, Kimak MA, Lawrence EC, et al. Candidate gene analysis in primary lymphedema. *Lymphat Res Biol.* 2008; 6:69–76. [PubMed: 18564921]
8. Finegold DN, Kimak MA, Lawrence EC, et al. Truncating mutations in FOXC2 cause multiple lymphedema syndromes. *Hum Mol Genet.* 2001; 10:1185–9. [PubMed: 11371511]
9. Karkkainen MJ, Ferrell RE, Lawrence EC, et al. Missense mutations interfere with VEGFR-3 signalling in primary lymphoedema. *Nat Genet.* 2000; 25:153–9. [PubMed: 10835628]