Our bodies’ tissues need continuous irrigation and drainage. Blood vessels feeding the tissues bring in the fluids, and drainage occurs via the lymphatic system. Whereas much is known about how blood vessels are built, the same was not true for lymph vessels. Now though, Norrmén et al. have identified two of the lead engineers that direct drainage construction—the transcription factors, Foxc2 and NFATc1 (1).

Previous studies found that mice lacking Foxc2 have malformed lymph vessels (2). Also, people with mutated Foxc2 suffer from severe limb swelling (lymphedema-distichiasis) caused by poor lymph drainage (3). Norrmén and colleagues have now found that Foxc2 specifically regulates a late stage of lymph development when large, valve-containing vessels arise from more primitive capillaries.

One characteristic of the malformed vessels in Foxc2-deficient mice is a lack of valves. “At the moment nothing is known [about] how lymphatic valves develop,” explained Tatiana Petrova, who led the study. The team therefore turned to proteins known to build heart valves to look for candidates that might cooperate with Foxc2 in the lymphatic system.

Only one of these candidates, NFATc1, showed expression in the developing lymph system of normal mice, and the factor was particularly abundant in lymph vessel valves. Mice lacking NFATc1 die at an embryonic stage before lymph valve formation—presumably due to failure of their heart and blood vessels, which develop earlier than the lymphatic system. To investigate the effect of NFATc1 on lymphatic valve development, the authors waited for normal mouse embryos to develop their circulatory system and then treated them with an NFAT inhibitor. The effect was very similar to that of mice that lack Foxc2. Supporting evidence for NFATc1’s involvement in lymph vessel development was published recently by a second group (4).

Norrmén and colleagues went further to show that Foxc2 and NFATc1 physically interact and that many DNA binding sites for the two transcription factors are closely linked. This latter discovery arose from a genome-wide search for Foxc2 binding sites and was somewhat of a nice surprise, according to Petrova. “We gave the Foxc2 data to bioinformaticians in Lausanne and they said, ‘Well you know there are NFAT binding sites highly enriched in your Foxc2 data’ and I think that was the most pleasant moment, actually, because they didn’t know anything about this NFAT stuff, and they just came independently saying, ‘Well it seems they might interact.’”

The bioinformaticians also came up with a consensus binding site for Foxc2, and a long list of target loci that might be controlled by the two transcription factors. The team now plans to investigate these targets as well as to work out the upstream molecular pathways controlling Foxc2 and NFATc1. It appears that the two factors are controlled by independent pathways—deficiency of one does not affect the other—and so it’s likely that they work synergistically to promote target gene expression.

Whatever the mechanism, if they can show that Foxc2 and NFATc1 also prompt lymph vessel regeneration in adults, boosting these factors could help patients with lymph drainage problems—including those that have suffered extensive tissue injuries, or have had lymph nodes removed as part of cancer treatment.

1. Norrmén, C., et al. 2009. J. Cell Biol. doi:10.1083/jcb.200901104.
2. Petrova, T.V., et al. 2004. Nat. Med. 10:974–981.
3. Ferrell, R.E. 2002. Ann. N. Y. Acad. Sci. 979:39–51.
4. Kulkarni, R. M., et al. 2009. Mech. Dev. doi:10.1016/j.mod.2009.02.003.