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INTESTINAL TRACT

DLL4 signalling maintains organization and function of lacteals

> “… adult lacteals … continuously encounter high mechanical stress, microbial products and dietary fat”

New molecular insights into maintenance and regeneration of lacteals, specialized lymphatic vessels in the villi of the small intestine, have been reported in a recent study published in *The Journal of Clinical Investigation*.

Although often overlooked in research, the intestinal lymphatic vasculature adopts key functions in the small intestine, regulates absorption and transport of fatty acids, and encourages an active crosstalk between immune cells in the area.

“Understanding mechanisms controlling these specialized blood and lymphatic vessels in adult organs where pathologies arise is critical for novel therapies,” explain first author Jeremiah Bernier-Latmani and corresponding author Tatiana Petrova.

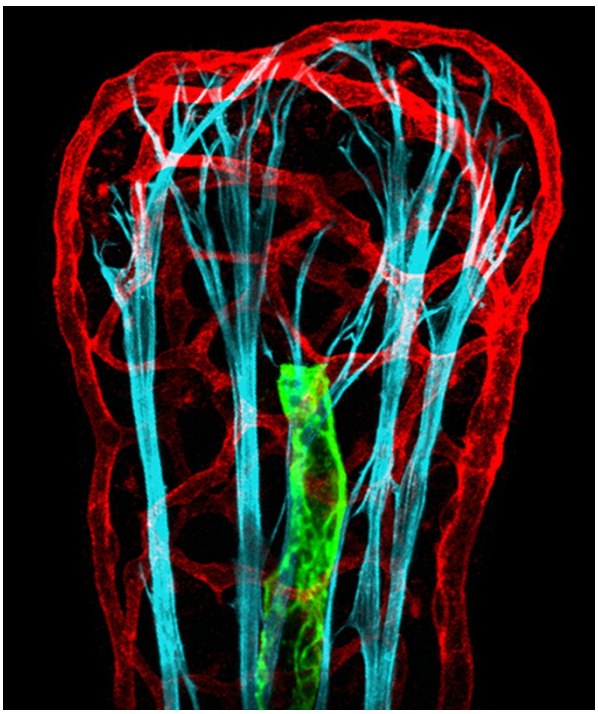

Image courtesy of J. Bernier-Latmani

Using a whole-mount immunostaining approach, the researchers analysed the stroma of small intestinal villi in mice and revealed a well-structured organization (see image) with blood capillaries that form cage-like patterns (red), interspersed with tree-like smooth muscle fibres (cyan) and lacteals (green) located within the centre. Immune cells, such as regulatory T cells and dendritic cells, were also found in close proximity of the smooth muscle cell fibres. Proliferation rates of lacteal lymphatic endothelial cells (LECs) in adult mice were low but steady (2.5% of $Ki67^+$ cells), whereas in embryonic skin ~30% of LECs were $Ki67^+$. Submucosal LECs were quiescent.

“We found that, surprisingly, adult lacteals are constantly and slowly regenerating, because they continuously encounter high mechanical stress, microbial products and dietary fat. Interestingly, such regeneration of lacteals parallels constant regeneration of intestinal epithelium,” the authors note.

In an attempt to decipher the molecular mechanisms involved in lacteal homoeostasis and regeneration, the investigators focussed on Notch signalling, which is known to regulate many aspects of endothelial physiology. They detected different levels of the Notch ligand DLL4 (delta-like protein 4) in arterioles (high), blood capillaries (intermediate) and venules (low) of intestinal villi. Tip cells of sprouting lacteals exhibited high DLL4 levels, indicating a potential role of DLL4 in lacteal function.

Deletion of *Dll4* in lymphatic vessels of adult mice resulted in a substantially shorter length of the lacteals, impaired LEC survival and reduced LEC migration. By contrast, inactivation of *Dll4* in blood vessels increased the number of filopodia and vessel branching. Using blocking antibodies, VEGFR3 and VEGFR2 signalling was confirmed as essential for *Dll4* expression and lacteal maintenance. Loss of *Dll4* also disrupted the organization of lacteal adherens junctions, probably resulting in impaired fat uptake.

“Overall, our work reveals how lymphangiogenic responses are shaped by tissue specialization and report a novel process for matching a unique need of intestinal lymphatic vessels both for continuous repair, and an efficient uptake of fat,” conclude the authors. Considering the important physiological roles of the intestinal lymphatic system, its dysregulation could also contribute to pathology. Future research will focus on additional molecular players involved in the specialization of intestinal lymphatic vessels and their crosstalk with other intestinal cells.

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ORIGINAL ARTICLE Bernier-Latmani, J. *et al.* DLL4 promotes continuous adult intestinal lacteal regeneration and dietary fat transport. *J. Clin. Invest.* doi:10.1172/JCI82045