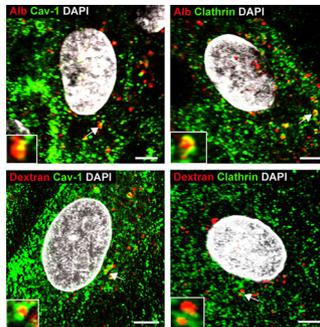


Flow-Induced Lymphatic Growth (p 1426)

Choi et al discover how tissue fluid flow prompts lymphatic vessel development.

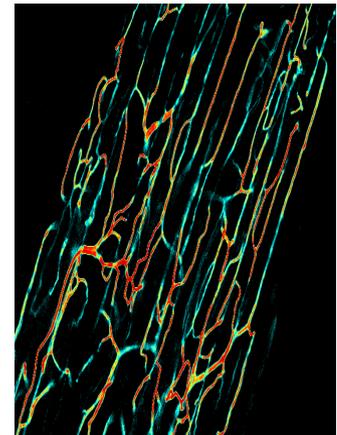
A fully functional lymphatic vasculature is essential for draining interstitial fluid and preventing tissue edema. Interestingly, research suggests that in the growing embryo the very presence and flow of fluid within tissues prompts lymph development. To understand how tissue fluids generate their own drainage system, Choi and colleagues focused on lymphatic endothelial cells (LECs), which give rise to the vessels. They showed that a steady laminar flow of culture medium over LECs, but not blood vessel ECs, induced these cells to proliferate. They also showed that proliferation-promoting transcription factors were upregulated in flow-treated LECs and that blocking the actions of these factors reduced flow-induced proliferation. Laminar flow is known to induce calcium influx in LECs, and the team went on to show that a plasma membrane calcium channel, called CRAC, was an integral link between laminar flow and proliferation, a link supported by the observation that knocking down a key component of the channel (a subunit called ORAI1) prevented the flow-activated proliferation of LECs. Moreover, in mice lacking functional ORAI1, lymph vessel density was reduced. Together, these results provide new insights into the development of the lymphatic system and may shed light on how, in certain lymphatic disorders, this process goes awry.



Transcellular Solute Transport in Lymphatics (p 1440)

Solutes travel to lymph vessels both through and between lymphatic endothelial cells, report Triacca et al.

The interstitial fluid in the body is continuously drained via lymphatic vessels, accumulating first in the nodes before eventually returning to the blood. This draining process has been thought to be largely passive—the result of hydrostatic pressure differences between the tissues and lymph vessels. Indeed, fluid flow into a vessel’s lumen was thought to occur primarily between the lymphatic endothelial cells (LECs), which form the vessel lining. However, there is little direct evidence to support this view, and recent evidence suggests that solute-filled vesicles could also transit across the LEC cytoplasm. To find out, Triacca and colleagues injected fluorescent albumin into the dermis of mouse ears and observed the protein’s passage to the lymph. They found that the albumin entered LECs, and in vitro studies confirmed that the protein was transported via vesicles. The team went on to show that solute uptake via this transcellular pathway was boosted by both increased fluid flow and the presence of inflammatory molecules. These results indicate that, in addition to passive paracellular transport, solute passage to the lymph can be actively controlled by LECs—a finding that could impact our understanding of the maintenance of tissue homeostasis, as well as the resolution of inflammation.



4D Analysis of Regenerative Angiogenesis (p 1453)

Arpino et al’s close examination of regenerating microvessels reveals flaws.

After an ischemic injury, the affected tissue undergoes rapid vasculogenesis. But it is unclear whether the newly regenerated vessels fully resemble the anatomy and function of normal vessels. To address this question, Arpino and colleagues decided to take a closer, more high-resolution look. Using a combination of intravital and confocal microscopy, they examined the regrowth of microvessels after hind limb ischemia in mice. They found that, although the vessels regenerated rapidly and robustly in the animals’ legs, the branching architecture of the vessels was aberrant, and the transit of red blood cells through the capillaries was slow, and disorderly, and did not respond adequately to local hypoxia. The researchers also found that smooth muscle cells surrounding the vessels did not form a continuous uniform layer as expected. These abnormalities persisted for several months after injury. The authors conclude that future therapeutic revascularization strategies must achieve more than just vessel regrowth if they are to restore tissue oxygenation in patients with ischemia.

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