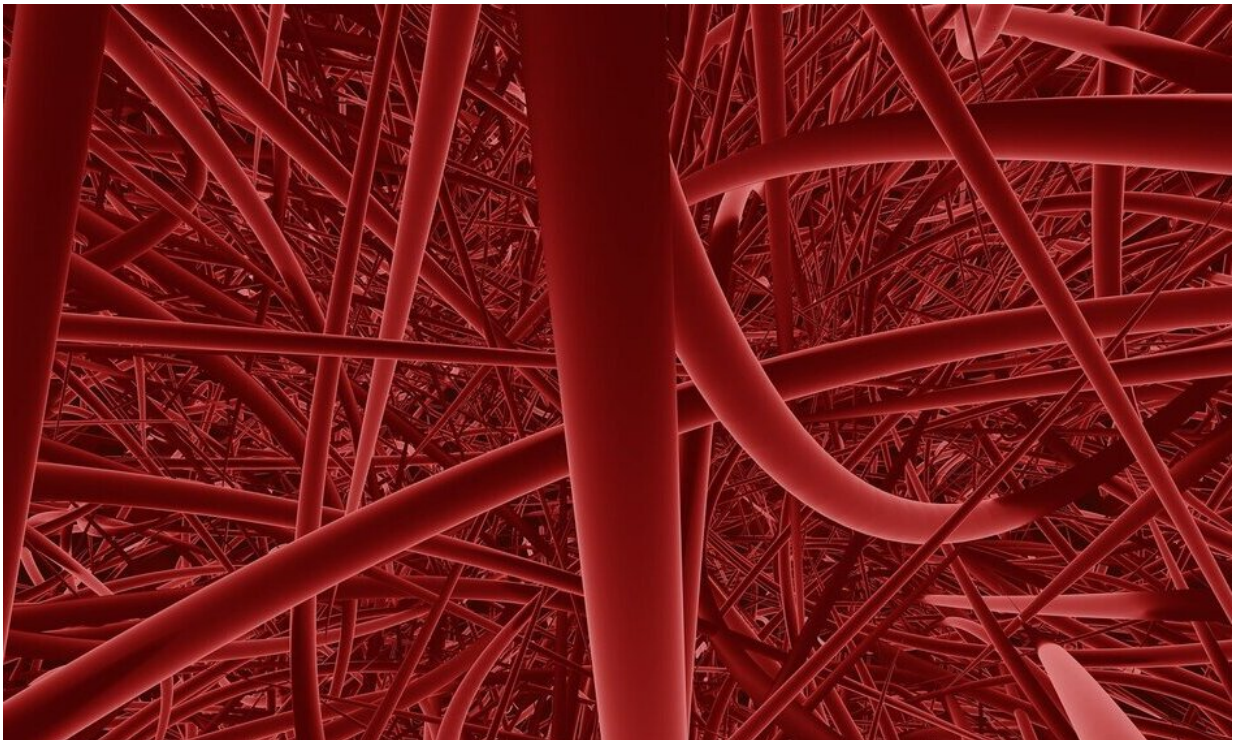


# Researchers find previously unknown role of primary cilia in vertebrate cells

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The primary cilium, an antenna-like subcellular structure ('organelle') protruding from the outside of many types of vertebrate cells, has an important but previously overlooked role in guiding the growth of lymphatic vessels, shows a new study. The authors show for the first time that mouse and human lymphatic endothelial cells (LECs), which

make up the inner and outer lining of lymphatic vessels, use primary cilia. They find that LEC primary cilia may direct the growth of a functional lymphatic network, not only during prenatal development, but also throughout life during inflammation and wound healing and in response to cancer. They show that mice in which the formation of primary cilia in LECs is prevented develop lymphatic vessels that are locally overgrown, suggesting that signals received by primary cilia may guide proper lymphatic vessel growth patterns. These results, published today in the open access journal *Frontiers in Cell and Developmental Biology*, have implications for human medicine.

"The first images were so exciting! LECs do have primary [cilia](#) and they are clearly important for patterning growth. The finding of a new regulatory 'hub' on LECs means that the way we think about how and what kind of signals are received by these cells has fundamentally changed. Targeting the assembly of cilia by the cell or their ways of signaling could allow us to control or stimulate lymphatic [vessel](#) growth in new ways," says corresponding author Dr. Darci M. Fink, an assistant professor at the Department of Chemistry and Biochemistry of South Dakota State University.

## **Lymphangiogenesis continues throughout life**

The lymphatic vessel system of vertebrates consists of hundreds of lymph nodes connected by a network of vessels spread throughout the body. Lymphatic vessels play a crucial role in health and homeostasis: they facilitate immune cell traffic during inflammation, drain excess fluid from the space between cells to [lymph nodes](#) and return it—clear of pathogens—to the bloodstream, and absorb fat molecules as an energy source. They first sprout during [embryonic development](#), but lymphangiogenesis, the growth of new lymphatic vessels, continues throughout life in an adaptive response to the microenvironment, in particular during inflammation and wound healing. Faulty

lymphangiogenesis can cause edema, impaired wound healing, chronic inflammation and tumor progression.

"Primary cilia are such an essential part of the function of many cell types, including those that form other tube-like structures like blood vessels, breast ducts and kidney tubules. Now, we can add lymphatic endothelial cells to that list. Understanding exactly how primary cilia govern LEC movement, division, and tube formation and how to exploit these mechanisms is the next exciting challenge," says Fink.

First, Fink and colleagues used microscopy to show that in tissue from healthy mice, primary cilia on LECs can protrude either from the outside of lymphatic vessels or face the interior cavity. The incidence of primary cilia is also particularly high on LECs at the tips of growing lymphatic vessels, where guiding cues are received. These findings suggest that LECs might use their cilia to interact with the microenvironment inside as well as outside lymphatic vessels, for example, sensing flow or the presence of soluble signaling molecules.

## **Disturbed prenatal development of lymph vessels after genetic knockout of IFT20**

Next, the authors used a well-established genetic cut-and-paste tool called Cre-Lox recombination to create a new transgenic line of mice, in which the key gene IFT20—necessary for the molecular assembly of cilia and transport of proteins as ciliary cargo—can be deactivated ('knocked out'). As predicted, the majority of LECs from these mice lacked a [primary cilium](#). The embryos showed significant edema, and the lymphatic vessels of the embryos were dilated and improperly branched, became surrounded by excess smooth muscle and inappropriately contained red blood cells. These results mean that the presence of a functional cilium on embryonic LECs is necessary for the

healthy prenatal development of the first lymphatic vessels.

## **Primary cilia are necessary for optimal lymphangiogenesis during disease**

Finally, Fink's group studied the importance of primary cilia for guiding lymphangiogenesis in adult mice, during inflammation, wound healing and tumor growth. To cause localized acute or recurrent inflammation, they used the so-called cornea inflammation bioassay, in which small synthetic sutures are inserted (under anesthetic and continuous pain control) in the cornea of the eye. This procedure is known to stimulate LECs present in lymphatic vessels at the edge of the cornea to sprout, divide and migrate toward the inflamed area, forming new lymphatic vessels. As predicted, this process was faulty in IFT20-knockout mice, where the network of new vessels became overgrown, too dense and with too many branches. The authors conclude that in the absence of primary cilia, lymphangiogenesis in response to disease is poorly regulated and results in new [lymphatic vessels](#) that aren't properly patterned.

"The striking overgrowth of lymphatic vessel seen after the loss of [primary cilia](#) points to the key role of cilia in coordinating the physiology of LECs with their microenvironment. The challenge now is to identify the signals sensed by lymphatic cilia. Across [eukaryotic organisms](#), cilia are known to use a wide range of signals such as small molecules, peptides, physical forces, osmotic changes, and light, so in principle lymphatic [cells](#) have many options for sensing," concludes co-author Prof. Gregory J. Pazour, University of Massachusetts Medical School.

**More information:** Delayna Paulson et al, Loss of Primary Cilia Protein IFT20 Dysregulates Lymphatic Vessel Patterning in Development and Inflammation, *Frontiers in Cell and Developmental*

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