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Story of lymphatic system expands to include chapter on valve formation

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A century after the valves that link the lymphatic and blood systems were first described, St. Jude Children's Research Hospital scientists have detailed how those valves form and identified a gene that is critical to the process.

The gene is Prox1. Earlier work led by Guillermo Oliver, Ph.D., a member of the St. Jude Department of Genetics, showed Prox1 was essential for formation and maintenance of the entire lymphatic vasculature. The lymphatic vasculature is the network of vessels and ducts that help maintain the body's fluid balance and serves as a highway along which everything from cancer cells to disease-fighting immune components moves. Oliver is senior author of the new study, which appeared in the October 15 edition of the scientific journal Genes *& Development*.

The new research suggests that Prox1 is also essential for proper formation of the one-way valves that control movement of fluid and nutrients from the lymphatic system into the blood stream. Researchers found evidence that the Prox1 protein also has a role in formation of the venous valves.

"Understanding how valves form is crucial to efforts to develop treatments for valve defects that affect both children and adults," said the paper's first author, R. Sathish Srinivasan, Ph.D., a research associate in the St. Jude Department of Genetics. Those defects are linked to a variety of problems including lymphedema and deep vein thrombosis,

which are blood clots that form deep in veins and have the potential for causing life-threatening complications. Lymphedema is the painful and sometimes disfiguring swelling that can occur when lymph flow is disrupted.

For more than a decade, the lymphatic system has been a focus of Oliver's laboratory. The laboratory's contributions through the years include evidence that leaky lymphatic vessels might contribute to obesity. Oliver and his colleagues also demonstrated how the lymphatic system forms from Prox1-producing cells destined to become lymphatic endothelial cells (LECs) when they leave the developing veins and migrate throughout the body.

The investigators also showed the Coup-TFII gene is essential to the process. The Coup-TFII protein binds to the promoter region of the Prox1 gene. The binding switches on production of the Prox1 protein that is required to create and maintain the lymphatic system. The newer research builds on that earlier work from Oliver's laboratory. The latest study focused on the lymphovenous valves. These valves are found at just two locations in the body, on either side of the chest just under the clavicle bone where the lymphatic vessels intersect with the subclavian and internal jugular veins.

Working in mice, investigators discovered that these lymphovenous valves form from a newly identified subtype of endothelial cell found in developing veins. Like the LECs that form the lymphatic system, the newly identified endothelial cells make Prox1. But while the LECs leave the veins and migrate throughout the body, these endothelial cells stay put to form the lymphovenous valves.

Researchers demonstrated the process requires two copies of the Prox1 gene. That ensures adequate levels of the Coup-TFII-Prox1 complex and with it enough Prox1 to build and maintain the lymphatic system. Mice

engineered to carry a single copy of Prox1 either did not survive or were born without lymphovenous and venous valves.

"If you have only one copy of Prox1 you are going to have a reduction in the Coup-TFII – Prox1 complex and so a dramatic reduction in the number of cells available to build the lymphatic system. That explains the defects we see," Srinivasan said.

Provided by St. Jude Children's Research Hospital