Time-lapse video reveals cells essential for 'birth' of blood stem cells

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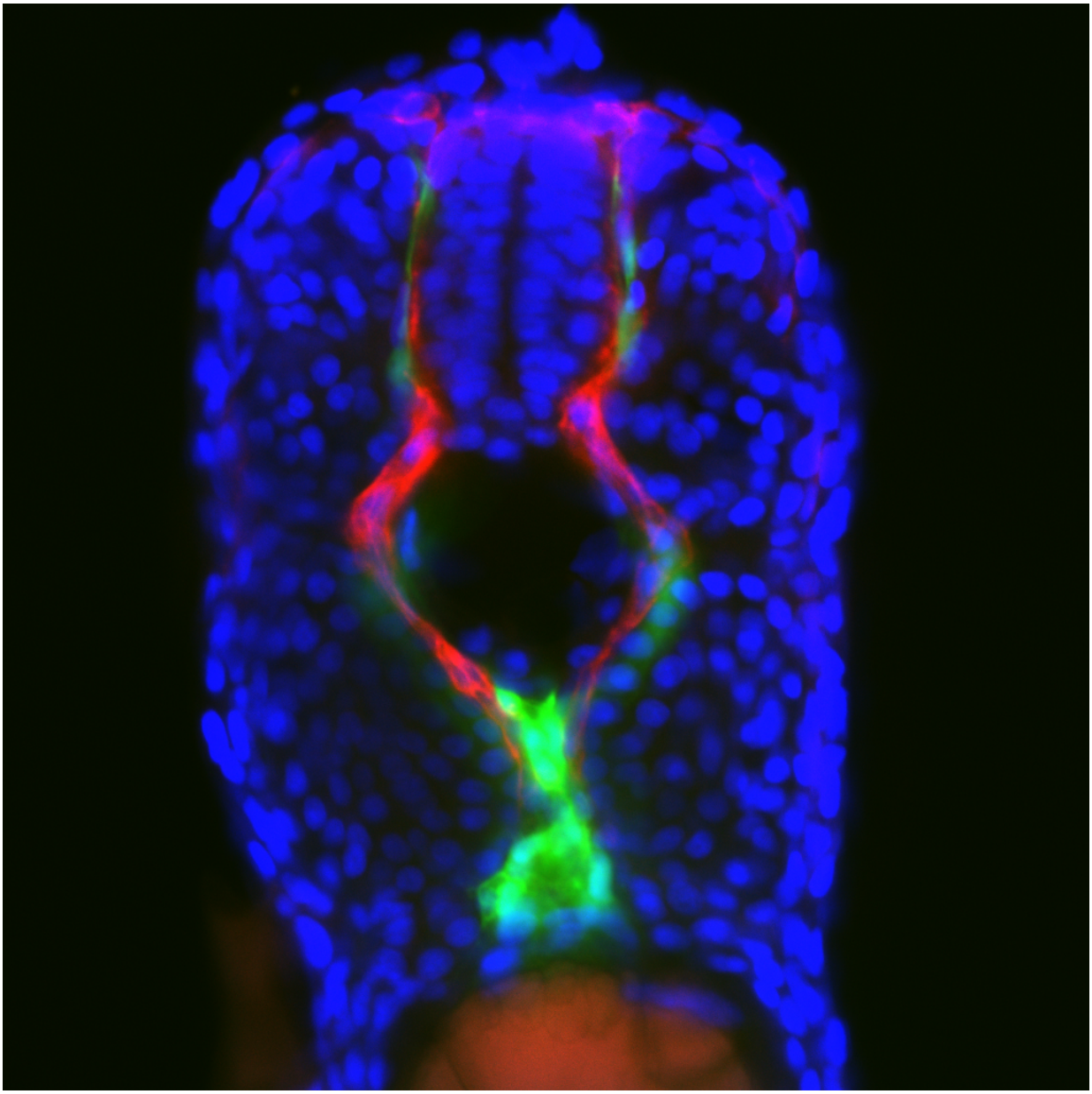

St. Jude researchers used time-lapse images to investigate the origins of blood stem cells in models like the example above. The image was fluoresced in order to help identify the cells involved. Credit: Erich Damm / St, Jude Children's Research Hospital

Like private investigators on a stake out, St. Jude Children's Research Hospital scientists used patience and video surveillance-like tools to identify cells that trigger blood cell development. The findings offer clues for making blood-forming stem cells in the laboratory that may ultimately help improve access to bone marrow transplantation.

"The research will likely open new avenues of investigation in stem cell biology and blood development and provide insight to aid efforts to make transplantable hematopoietic stem cells in the lab," said corresponding author Wilson Clements, Ph.D., an assistant member of the St. Jude Department of Hematology. The research appears today in the journal *Nature Cell Biology*.

Blood-forming stem cells are capable of making any type of blood cell in the body. They are also used in transplant therapies for cancers like leukemia or other blood diseases like sickle cell. They are starting to be used to deliver gene therapy. However, a shortage of suitable donors limits access to treatment, and efforts to produce blood from pluripotent stem cells in the laboratory have been unsuccessful. Pluripotent stem cells are the master cells capable of making any cell in the body.

All blood-forming stem cells normally arise before birth from certain endothelial cells found in the interior blood vessel lining of the developing aorta. This process—including how endothelial cells are set on the path to becoming blood stem cells—is not completely understood.

Clements and first author Erich Damm, Ph.D., a St. Jude postdoctoral fellow, have identified trunk neural crest cells as key orchestrators of the conversion of endothelial cells to blood stem cells. Trunk neural crest cells are made in the developing spinal cord and migrate throughout the embryo. They eventually give rise to a variety of adult cells, including neurons and glial cells in the sympathetic and parasympathetic nervous system, which control feeding, fighting, fleeing and procreating.

Using time-lapse video, the researchers tracked the migration of neural crest cells in the transparent embryos of zebrafish. Zebrafish and humans share nearly identical blood systems, as well as the programming that makes them during development. After about 20 hours, the neural crest cells had reached the developing aorta. After hour 24, the migrating cells had cozied up to the endothelial cells in the aorta, which then turned on genes, such as runx1, indicating their conversion to blood stem cells.

The investigators used a variety of methods to show that disrupting the normal migration of neural crest cells or otherwise blocking their contact with the aorta endothelial cells prevented the "birth" of blood stem cells. Meanwhile, other aspects of zebrafish development were unaffected.

"Researchers have speculated that the endothelial cells that give rise to blood-forming stem cells are surrounded by a support 'niche' of other cells whose identity and origins were unknown," Damm said. "Our results support the existence of a niche, and identify trunk neural crest cells as an occupant."

Adult bone marrow includes niches that support normal function and notably feature cells derived from trunk neural crest cells.

The findings also suggest that trunk neural crest cells use a signal or signals to launch blood stem cell production during development. The

researchers have eliminated adrenaline and noradrenaline as the signaling molecules, but work continues to identify the signaling proteins or small molecules involved.

More information: Pdgf signalling guides neural crest contribution to the haematopoietic stem cell specification niche, *Nature Cell Biology* (2017). nature.com/articles/doi:10.1038/ncb3508

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