Why we make blood cells in our bones

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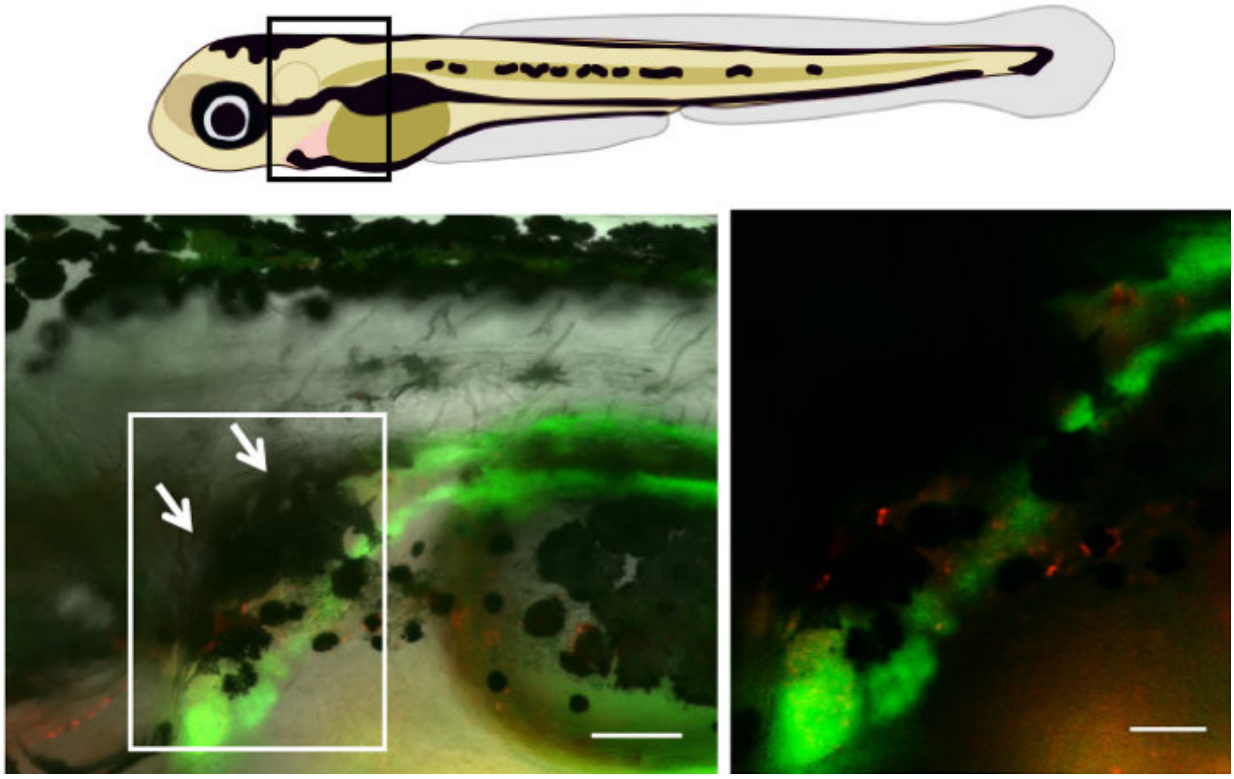


In a zebrafish larva (illustration above), a dark umbrella formed by pigmented cells (white arrows point to these black spots in box, left) in the kidney protects vulnerable stem cells from damaging UV light. Right image is a closeup of the box. Scale bars equal 100 micrometers (left) and 50 micrometers (right). Credit: F. Kapp et al./*Nature* 2018

In humans and other mammals, the stem cells that give rise to all blood

cells are located in the bone. But in fish, blood stem cells are found in the kidney. Since the late 1970s, when biologists first realized that blood develops in a specific location in the body—the 'blood stem cell niche'—they have wondered why different creatures have evolved to carry out this function in different locations.

Forty years later, scientists have found a valuable clue: the niche evolved to protect blood stem cells from the harmful ultraviolet (UV) rays in sunlight.

The findings are published in *Nature* by researchers at the Harvard Department of Stem Cell and Regenerative Biology, Boston Children's Hospital's Stem Cell Program, and the Harvard Stem Cell Institute. This new piece of the 'blood stem cell niche' puzzle will help the team improve the safety of blood stem cell transplants.

A parasol above the kidney

The inspiration for this study came from an incidental observation in the zebrafish, an animal model used in many laboratories.

"I was trying to look at blood stem cells under the microscope, but a layer of melanocytes above the kidney blocked my view," said Friedrich Kapp, M.D., now at the Center for Pediatrics, University of Freiburg Medical Center in Germany. Melanocytes are cells that produce melanin, the pigment responsible for the color of human skin.

"The shape of the melanocytes above the kidney reminded me of a parasol, so I thought, do they provide UV protection to blood stem cells?" said Kapp.

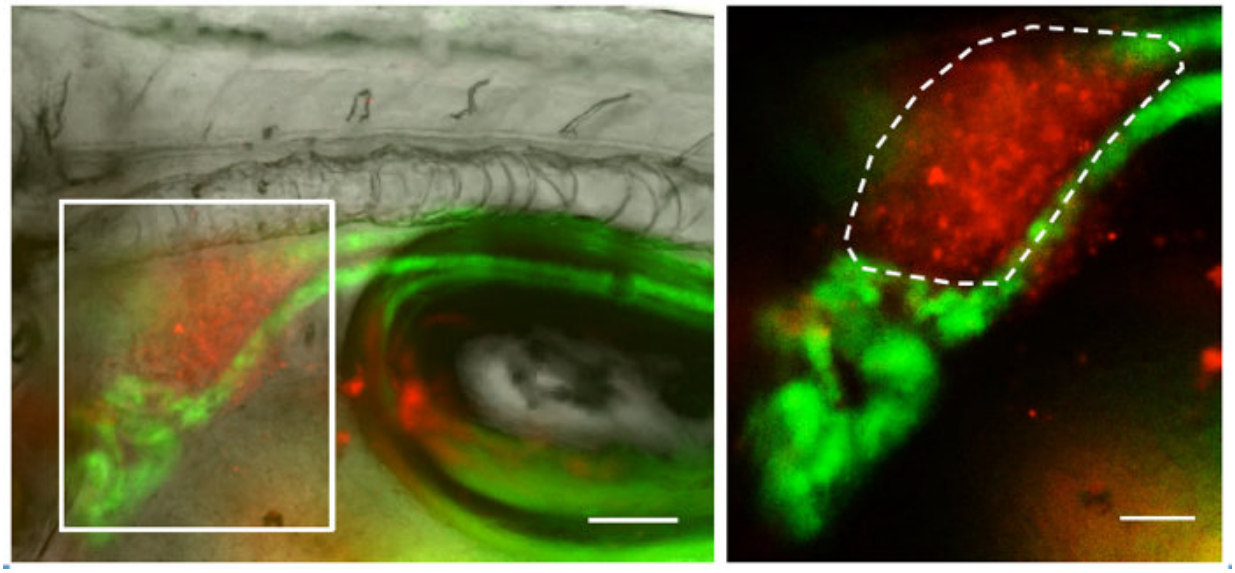
So Kapp exposed normal zebrafish and mutant zebrafish lacking melanocytes to UV radiation. Sure enough, the number of blood stem

cells decreased in the mutants.

Moreover, the normal zebrafish lost blood stem cells when they were turned upside down and irradiated. This confirmed that the melanocyte umbrella was physically shielding the kidney from the rays above.

From water to land

After showing that melanocytes protect blood stem cells from UV radiation, the researchers searched the evolutionary 'tree of life' to find similarities. They found that melanocytes have been surrounding the blood stem cell niche for a long time—even in a fish species that separated from the rest of the vertebrate family trees around 500 million years ago.



A zebrafish larva lacking the protection of a pigmented cell umbrella leaves kidney stem cells (red) exposed to UV light. Right image is a closeup of the box. Scale bars equal 100 micrometers (left) and 50 micrometers (right). Credit: F. Kapp et al./*Nature* 2018

Looking at more recent evolution, toward land animals, the researchers zoomed in on a type of poison dart frog. When the tadpoles grew legs, the blood stem cells moved from the melanocyte-covered kidney to the bone marrow. The researchers noticed that during all its developmental stages, the frog's blood stem cell niche was protected from UV light.

Understanding the blood stem cell niche

"We now have evidence that sunlight is an evolutionary driver of the blood stem cell niche," said Leonard Zon, M.D., senior author of the study. Zon is a Harvard professor of stem cell and regenerative biology, the Grousbeck Professor of Pediatrics at Boston Children's Hospital, and a Howard Hughes Medical Institute Investigator.

Zon will continue to study the blood stem cell niche by defining the biological signaling pathways that govern the interactions between melanocytes and blood stem cells.

A better understanding of the niche is important for blood stem cell transplants, where it is critical for transplanted cells to find a new, safe home in the body.

"As a hematologist and oncologist, I treat patients with blood diseases and cancers," said Zon. "Once we understand the niche better, we can make blood stem cell transplants much safer."

More information: Friedrich G. Kapp et al, Protection from UV light is an evolutionarily conserved feature of the haematopoietic niche, *Nature* (2018). DOI: 10.1038/s41586-018-0213-0

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