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Stem cells leave blood vessels in areas of the bone marrow with low blood flow

Hematopoietic stem cells adhere to net-like blood vessels and transmigrate

The treatment of leukaemia and some cancers involves killing the blood stem cells of the diseased bone marrow and replacing them through the transplantation of healthy stem cells. The new stem cells are transferred to the recipient's bloodstream via a venous catheter and find their own way to the bone marrow. It is not exactly known where and how these hematopoietic stem cells identify suitable locations in the blood marrow vessels where they can leave the bloodstream. Using a state-of-the-art laser microscope, researchers from the Max Planck Institute for Molecular Biomedicine in Münster observed and measured the blood flow dynamics in intact bone marrow vessels *in vivo* in great detail. This enabled them to identify the blood flow conditions under which blood stem cells migrate from the vessels and can seek a niche in the bone marrow.

Bone marrow contains countless blood vessels, and is well supplied with blood and oxygen as a result. Scientists assume, however, that hematopoietic stem cells - blood stem cells - can only settle permanently if the oxygen tension in the bone marrow niche is low. In order to study the network of blood vessels and the perfusion rate in bone marrow microvessels in detail – and in conditions as close to nature as possible – the Max Planck scientists developed a microscopy method which enables them to observe the blood flow in the intact bone marrow microvasculature *in vivo*. "Using our multiphoton microscope, we can not only observe deep areas in the intact living tissue non-invasively, we can also make the fibre structure of the bone collagen visible without dye staining. But it was not until we upgraded our laser microscope that we succeeded in recording rapid serial images of the blood flow and observing how the blood cells shoot through the vessels. In this way we created a kind of live animation of the blood flow in the different types of vessels," explains Gabriele Bixel, first author of the study.

Because the thigh bone is relatively thick, Bixel and her colleagues focused on the cranial bone instead. "Mice have thin skulls and their blood vessels are relatively accessible," says Bixel. "These are optimal conditions for looking through the bone to the blood vessels concealed below it in their bone marrow cavities. Moreover, the dynamic flow behaviour of the blood through the different types of bone marrow vessels can be made visible with the help of an optical contrast agent."

Using fluorescent antibodies, the scientist were able to show that blood vessels in the cranial bone marrow are similar in appearance to those found in the thigh bone. "To our surprise we observed that a certain type of blood vessel in the bone marrow forms a mesh in which the blood flow is heterogeneous and, in fact, minimal in some cases." Where there is little flow, there are not many flow-related shear stresses: "Thanks to the low flow velocities, approaching hematopoietic stem cells can adhere to the vessel wall and then migrate to the bone marrow," says Bixel. The live recordings document how, within hours of being transplanted, the hematopoietic stem cells attach themselves to the inner vessel walls in the bone marrow and start to migrate into the surrounding tissue – their niche. After approximately 24 hours, most of the stem cells have slipped through the vessel wall and are largely stationary in the bone marrow.

Most of the molecular and cellular processes are still unclear. Does the stem cell determine the location of migration alone or do the cells of the inner vessel wall also play an active role in this process? What does the stem cell exactly do in their niche after migration is also unknown. What is clear, however, is that this new microscopy method will enable the scientists to make progress in finding answers to these important questions.

Original publication:

M. Gabriele Bixel, Anjali P. Kusumbe, Saravana K. Ramasamy, Kishor K. Sivaraj, Stefan Butz, Dietmar

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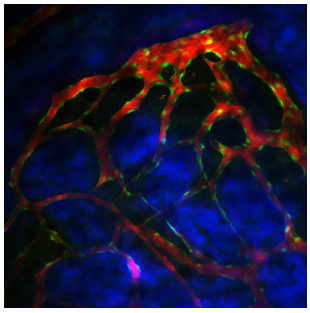
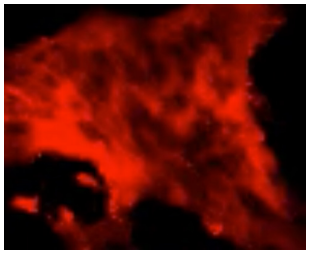


Mesh-like network of blood vessels in their bone marrow cavities

Different types of blood vessels in the bone marrow have different functions. Within this dense network, blood stem cells find the optimal conditions for migrating to the surrounding tissue (red: blood plasma; green: blood vessels; blue: bone marrow tissue)

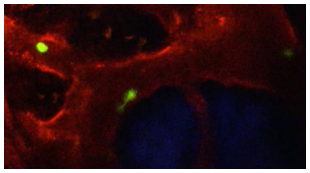
mpimuenster_homing.jpg
Credit: MPI Münster / Gabriele Bixel



Live and in colour: computer animation of the blood flow in the bone marrow

Large numbers of red blood cells flow throw a bone marrow vessel (Red: blood plasma; black: red blood cells)

mpimuenster_blood-flow_Bixel.mp4
Credit: MPI Münster / Gabriele Bixel



Migration of blood stem cells to their niche in the bone marrow

Rolling and adhering blood stem cells during migration in the bone marrow blood vessels (red: blood vessels; green: blood stem cells; blue: bone tissue)

mpimuenster_homing_Bixel.mp4
Credit: MPI Münster / Gabriele Bixel