Blood stem cells fight invaders, study finds

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No other stem cell is more thoroughly understood than the blood, or hematopoietic, stem cell. These occasional and rare cells, scattered sparingly throughout the marrow and capable of replenishing an entire blood system, have been the driving force behind successful bone marrow transplants for decades. Scientists, for the most part, have seen this as the hematopoietic stem cell's (HSC) singular role: to remain in the bone marrow indefinitely and to replenish blood and immune system cells only when called upon.

New research from the lab of Harvard Medical School professor of pathology Ulrich von Andrian, published in the November 30 edition of *Cell*, now suggests that HSCs' biological role is far more versatile and dynamic. He and his colleagues have found that HSCs can travel from the bone marrow, through the blood system, and enter visceral organs where they perform reconnaissance missions in search of pathogenic invaders. Upon encountering an invader they immediately synthesize a defense, divide and mature, churning out new immune system cells such as dendritic cells and other leukocytes, right on the spot.

"This process changes the way we look at blood stem cells," says von Andrian.

For almost five decades scientists have known that a fraction of HSCs will sometimes migrate from the bone marrow into the bloodstream. And while scientists have observed this phenomenon, they haven't known exactly why the stem cells would do this, and what sort of itinerary they might follow once they entered the blood.

A group in von Andrian's lab, led by postdoctoral researcher and cardiologist Steffen Massberg, decided to explore this question.

They began be extracting lymph samples from the thoracic duct of a mouse. The thoracic duct, a major component of the lymphatic system, routes the body's excess fluids into the circulation, fluids that normally accumulate in organs. In that sense, it's a kind of physiological storm drainage system. The group reasoned that any itinerary would eventually bring these cells into the lymph system, so it marked a logical starting point.

After screening large samples of thoracic fluid, they discovered an extremely small population of cells that, after rigorous testing, behaved identically to blood stem cells. Further tests, which involved mice genetically engineered so that their blood stem cells could be detected through fluorescent microscopy, revealed that these cells were also scattered throughout visceral organs, such as liver, heart, and lung.

"Taken all together, a picture developed suggesting that these cells migrated from the marrow and into the circulation where they would then leak out and enter the tissue," says Massberg. "After that, the thoracic duct would empty them back into the circulation, where they could reenter the marrow. But the question was, why" What exactly are they doing""

The group had found that the stem cells remain in the tissue for thirty-six hours before exiting into the thoracic duct. This suggested that they were conducting some kind of surveillance. To test this, Massberg and his colleagues injected a bacterial endotoxin into the mouse tissue. Within a matter of days, clusters of specialized immune cells formed in the infected areas.

"Typical immune responses deplete local specialized immune cells," says

Massberg. “It appears that the hematopoietic stem cells initiate an immune response and replenish these specialized immune cells. It’s a way of sensing local environmental disturbances and responding locally.”

But finally, the researchers identified the molecular mechanism that explained these observational data.

After residing for a while in the organ tissue, the stem cells receive a lipid signal that enables them to exit into the thoracic duct. However, the presence of endotoxin disrupts the normal signaling cascade. When the receptors on the stem-cell surface that detect the pathogens become active, the cell’s ability to receive the lipid signal is blocked. The stem cells literally get stuck in the tissue, where they are then triggered to proliferate into immune cells.

“That stem cells are actually a part of the immune system, rather than just giving rise to it, is a very provocative idea,” says von Andrian. “This opens up a number of new avenues for us to explore ways that our bodies fight pathogens.”

The researchers are now looking at ways that other common diseases, like cancer, may exploit this process.

Source: Harvard Medical School