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Unexpected reservoir of monocytes discovered in the spleen

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It takes a spleen to mend a broken heart - that's the conclusion of a surprising new report from researchers at the Massachusetts General Hospital (MGH) Center for Systems Biology, directed by Ralph Weissleder, MD, PhD. In the July 31 issue of *Science* the team reports how, in following up an intriguing observation, they discovered an unexpected reservoir of the immune cells called monocytes in the spleen and went on to show that these cells are essential to recovery of cardiac tissue in an animal heart attack model.

"Monocytes are known to serve as a central defense system against injury, and we found that monocytes released from the spleen go directly to the injured heart and participate in wound healing," says Matthias Nahrendorf, MD, PhD, a co-lead author of the study.

Monocytes are generated in the bone marrow, released into the blood and are known to accumulate at injured or infected tissues, where they differentiate into macrophages or dendritic cells. In investigating processes involved in the healing of ischemic heart tissue - the sort of injury produced in a heart attack - in mice, the research team was surprised to find more monocytes accumulating at the site of injury than would be found in the animals' entire circulatory system. When they searched many types of tissue for the presence of cells with monocyte-specific molecules, they only found significant numbers of such cells in the spleen.

Monocytes in the spleen were identical in appearance, composition and

function to monocytes in the blood. To investigate the splenic monocyte reservoir's potential involvement in cardiac healing, the researchers used several new technologies. A newly developed microscopic technique allowed them to determine how and where monocytes are stored in the spleen - previously known to store red blood cells - and to study how monocytes are released in response to an experimentally-induced heart attack. A novel three-dimensional optical imaging technique (fluorescence molecular tomography, developed at the MGH Center for Molecular Imaging Research) allowed study of monocyte-mediated immune functions at the site of heart muscle injury.

In mice whose spleens were removed and replaced with a donor organ, an induced heart attack led to rapid increase of spleen-derived donor monocytes in the bloodstream and massive accumulation of donor cells at the site of injury. In animals from whom spleens were removed but not replaced, heart attack produced no significant monocyte increase in the bloodstream or in the heart. "With all these approaches together, we found that the monocytes that travel to the heart after a heart attack come directly from the spleen and that, without the splenic monocytes, the heart tissue does not heal well," says Filip Swirski, PhD, co-lead author of the *Science* report.

The investigators also found that the hormone angiotensin II, known to be released in response to a heart attack, is actively involved in the release of monocytes from the spleen. Identifying that pathway could lead to ways of manipulating the splenic monocyte reservoir to improve healing after a heart attack and potentially regulate other inflammatory situations. "We need to know whether this monocyte reservoir is important in other diseases - such as viral or bacterial infection, cancer or atherosclerosis - and understand how to precisely control storage and release of monocytes in a therapeutic setting, both of which we are currently investigating," says Mikael Pittet, PhD, senior author of the *Science* report.

Source: Massachusetts General Hospital (news : web)