Investigators in the MGH Center for Systems Biology have discovered a previously unknown type of immune cell, a B cell that can produce the important growth factor GM-CSF, which stimulates many other immune cells. They also found that these novel cells may help protect against the overwhelming, life-threatening immune reaction known as sepsis.

Newly identified type of immune cell may be important protector against sepsis

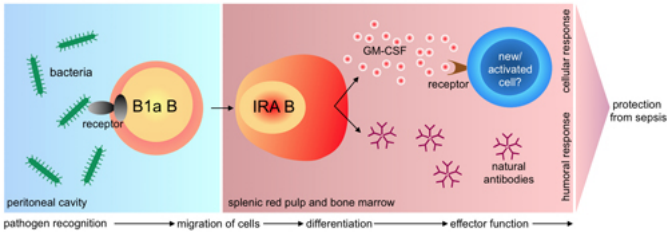
12/Jan/2012

Investigators in the Massachusetts General Hospital (MGH) Center for Systems Biology have discovered a previously unknown type of immune cell, a B cell that can produce the important growth factor GM-CSF, which stimulates many other immune cells. They also found that these novel cells may help protect against the overwhelming, life-threatening immune reaction known as sepsis.

"B cells are a family of white blood cells that secrete antibodies, and GM-CSF induces the production or activation of granulocytes and macrophages, other white blood cells that have specific roles in the immune system," says Filip Swirski, PhD, of the MGH Center for Systems Biology, senior author of the report that is to be published in the journal *Science* and is receiving advance release on the Science Express website. "Our findings are surprising not only because B cells were not previously known to produce GM-CSF in vivo but also because they indicate these novel cells initiate an important immune response."

As part of a separate investigation, Swirski and his team analyzed production of GM-CSF (granulocyte macrophage colony-stimulating factor) in tissue from several important organs. They were surprised to find that application of a bacterial molecule known to produce a powerful immune response induced GM-CSF production by what turned out to be a previously unknown family of B cells in the spleen. Because GM-CSF is known to activate white blood cells as part of the innate immune response – the body's first line defence against pathogens – the novel cells were named innate response activator (IRA) B cells.

The researchers went on to identify distinguishing characteristics of IRA-B cells, including gene expression patterns not seen in other B cells. They also determined that IRA-B cells derive from B cells known as B1a B cells. These IRA-B cell precursors originally reside in the peritoneal cavity but, after detecting the presence of invading bacteria, travel to the spleen or bone marrow where they differentiate into IRA-B cells that can either produce antibodies or release GM-CSF.



Development and function of innate response activator (IRA) B cells
The precursors of IRA-B cells, B1a B cells, reside in the peritoneal cavity. When B1a cells recognize bacteria infecting the peritoneal cavity, they migrate out of the peritoneal cavity, accumulate in the red pulp of the spleen or the bone marrow, and become IRA-B cells that secrete abundant amounts of GM-CSF. This growth factor acts on cells expressing its receptor, arming the innate immune response for efficient bacterial clearance. (image credit: Filip Swirski, PhD, MGH Center for Systems Biology)

"While the IRA-B cell shares many attributes with other B cells, it is unique in its involvement with GM-CSF production," explains Clinton Robbins, PhD, co-lead and co-corresponding author of the *Science* article. "Instead of the classic way that B cells recognize antigens, B1a B cells produce IRA-B cells after recognizing bacteria via a type of receptor known to be involved in the first steps of inflammation. The IRA-B cell, therefore, appears to be an early orchestrator of the immune system."

To test the potential role of IRA-B cells in sepsis, the researchers developed a mouse model in which B cells were totally unable to produce GM-CSF, preventing the generation of IRA-B cells. Those mice were unable to mount a defense against induced sepsis and died much earlier and in greater numbers than did control animals. Inflammatory markers in the infected mice lacking IRA-B cells suggested a defect in the ability to clear bacteria.

"We think that IRA-B cells sound a distress call when they deliver GM-CSF to the spleen, an organ where cells known to be important to the recognition and clearance of bacteria reside," explains Swirski, an immunologist who is an assistant professor of Radiology at Harvard Medical School. "Sepsis is an immunological conundrum. On the one hand it results from failure of the immune system to control infection. On the other hand, immune cells that do respond inflict damage and contribute to complications such as leakage of blood vessel walls and septic shock. Striking a balance between controlling infection and controlling inflammation is a major therapeutic goal, and we believe the IRA-B cell is a critical, previously unrecognized component in that balance."

Additional co-lead authors of the *Science* report are Phillipp Rauch, MS, and Aleksey Chudnovskiy, MS, of the MGH Center for Systems Biology. Other co-authors are Ralph Weissleder, MD, PhD, director of the MGH Center for Systems Biology; Georg F. Weber, MD, PhD, Martin Etzrodt, MS, Ingo Hilgendorf, MD, Elizabeth Tiglao, Jose-Luiz Figueiredo, MD, Yoshiko Iwamoto, Igor Theurl, MD, Rostic Gorbatov, Mikael J. Pittet, PhD, and Matthias Nahrendorf, MD, PhD, MGH Center for Systems Biology; Michael Waring and Adam Chicoine, Ragon Institute of MGH, MIT and Harvard; and Majd Mouded, MD, University of

Pittsburgh. The study was supported by grants from the National Institutes of Health, the Boehringer Ingelheim Foundation and the American Heart Association.

Massachusetts General Hospital, founded in 1811, is the original and largest teaching hospital of Harvard Medical School. The MGH conducts the largest hospital-based research program in the United States, with an annual research budget of more than $750 million and major research centers in AIDS, cardiovascular research, cancer, computational and integrative biology, cutaneous biology, human genetics, medical imaging, neurodegenerative disorders, regenerative medicine, reproductive biology, systems biology, transplantation biology and photomedicine.

Media Contacts: Sue McGreevey, smcgreevey@partners.org, 617 724-2764