

Gaining in the Battle Against Sepsis

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Sepsis is a body-wide toxic response to an overwhelming infection. It kills about 215,000 Americans each year, and its incidence is rising ([Sepsis Alliance](#)). The lack of understanding about its pathophysiology can overwhelm physicians as much as the disease itself overwhelms its victims. Recently, a research team led by Dr. Filip K. Swirski, of the Center for Systems Biology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, published a study that considerably increases our understanding of and may lead to more effective therapies against sepsis ([Rauch et al. 2012](#)).

Surprise: a new B cell type

The Swirski team's research began with an interest in understanding the function of a growth factor called granulocyte macrophage colony stimulating factor (GM-CSF). This factor's role in sepsis was enigmatic: depending on the circumstances, either its ablation or supplementation is mitigating. So, Swirski and his colleagues profiled the expression of GM-CSF in C57BL/6J (B6J, [000664](#)) mice. They were surprised to find that most of the cells that express the factor reside in the bone marrow and spleen. The number of these cells increases (especially in the spleen) in response to lipopolysaccharide (LPS), a bacterial molecule that elicits strong immune responses in animals. The Swirski team was also surprised to find that these cells are B cells. Until then, GM-CSF was thought to be produced only by non-hematopoietic cells, macrophages, and, sometimes, T cells. Swirski and his colleagues found that these cells have a unique transcriptome and are phenotypically and functionally distinct from other B cells. They dubbed them "innate response activator B" (IRA-B) cells. They found that the number of IRA-B cells increases in the spleens of B6J mice challenged with either a sepsis model or *E. coli*, indicating that IRA-B cell expansion is a response to bacterial infection.

The origin of IRA-B cells

By performing a series of parabiosis, fate-mapping, and adoptive transfer experiments, the Swirski team determined that IRA-B cells originate from a circulating subset of B cells called B1a B cells. They determined that these B1a B cells originate in the peritoneum and, in response to [TLR stimuli](#), enter the circulation and relocate to the spleen, where they differentiate into IRA-B cells. The researchers wanted to identify the biochemical pathways that mediate the conversion of B1a B to IRA-B cells. They found that IRA-B cells cannot be produced by the following five knockout mouse strains:

- B cell-deficient B10.129S2(B6)-*Ighm*^{tm1Cgn}/J (μMT, [002249](#)) mice
- *Cd19*-deficient B6.129P2(C)-*Cd19*^{tm1(cre)Cgn}/J mice ([006785](#)), which lack B-1 lymphocytes
- *Tlr4*-deficient B6.B10ScN-*Tlr4*^{lps-del}/JthJ mice ([007227](#)), which lack the LPS receptor TLR4 (and therefore exhibit a defective response to LPS)
- *Myd88*-deficient mice, which lack the TLR4 adaptor MYD88
- *Tnfrsf13c*-deficient B6(Cg)-*Tnfrsf13c*^{tm1Mass}/J mice ([007212](#)), which lack the B cell-activating factor receptor (BAFFR)

Further experiments with *Tlr4*-deficient mice led the researchers to conclude that direct TLR4 signaling on B1a B cells is sufficient to generate IRA-B cells. Other experiments revealed that GM-CSF produced by IRA-B cells serves as an autocrine factor that helps convert B1a B cells to IRA-B cells. Swirski and his colleagues also found that, to keep from being shuttled away from the spleen by the circulatory system, IRA-B cells rely on the cell adhesion ligands (integrins) VLA4 and LFA1

Together, these results indicated that, during sepsis, bacterial proteins activate TLR4-, MyD88-, and BAFFR-dependent pathways in peritoneal B1a B cells. These cells enter the circulation and travel to the spleen. There, under the influence of GM-CSF, they differentiate into IRA-B cells.

The function of IRA-B cells

Once they knew how IRA-B cells originate, Swirski and his colleagues wanted to know how they function. So, they generated IRA-B-null mice and challenged them with sepsis. They found that these mice die within two days, much faster than normal mice. They exhibit an excess number of peritoneal leukocytes, severe cytokine storm in the serum and peritoneum, high bacterial loads and poor bacterial phagocytosis, low serum IgM levels, and severe liver and lung damage. These results indicated that IRA-B cells mitigate septic shock by mediating bacterial clearance.

In summary, the Swirski team demonstrated that GM-CSF is an autocrine, pleiotropic cytokine produced by a previously unidentified and unique subset of B cells called IRA-B cells. They characterized the biochemical pathways that mediate B1a to IRA-B cell conversion and increased our understanding of the innate immune system's response to sepsis. Their findings may lead to more effective therapies for treating sepsis and other infectious diseases.

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