

Surprising Cells Stymie Sepsis

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Sepsis isn't just one of those old-time diseases that people used to die from before the discovery of antibiotics. It's still a major killer. Now, a new study shows that immune cells known as B cells forestall sepsis in mice, a discovery that may help researchers devise better treatments for the illness.

Each year, up to 1 million people in the United States fall victim to sepsis, a runaway infection coupled with bodywide inflammation. Despite antibiotics and other treatments, about 25% of sepsis patients die, notes infectious disease researcher Steven Opal of Brown University, who wasn't involved with the study. "Sepsis is a huge problem that we've had great difficulty solving," he says.

At first glance, B cells don't look like part of the solution. Their most familiar job is to pump out defensive proteins called antibodies. Immunologist Filip Swirski of Harvard Medical School in Boston and colleagues discovered the cells' involvement in sepsis by accident. Swirski has been probing the role of immune cells called macrophages in cardiovascular disease. He and his colleagues were trying to pin down the cells that manufacture granulocyte macrophage colony stimulating factor (GM-CSF). This protein exerts a big influence on white blood cells, spurring some of them to mature and switching on pathogen-fighters such as neutrophils. Swirski says that researchers thought that macrophages or other non-B cells were the source of GM-CSF. Yet in mice, the team found, most of the GM-CSF-making cells in the spleen were B cells. These cells, which the researchers dubbed innate response activator (IRA)-B cells, were unique. Their cell membrane bristled with a combination of proteins not seen on other B cells. Furthermore, B cells typically sense trespassing microbes by using the B cell receptor, a protein found only on their surface, whereas IRA-B cells rely on the same proteins that are prevalent on macrophages and other body cells.

One situation where GM-CSF might be important is sepsis—although studies conflict about whether it is harmful or beneficial. To gauge the effects of IRA-B cells, the researchers studied mice that developed sepsis because of an intestinal puncture. [Mice that lacked the B cells died, whereas 40% of the control animals that had plenty of the cells survived.](#) Swirski and colleagues report online today in *Science*. The IRA-B cell "is a specialized GM-CSF producer in the context of infection," Swirski says.

The study isn't the first to suggest that B cells curb sepsis—a paper published last summer also reached that conclusion, but it didn't identify which brand of B cells provides the benefit or how they help. Swirski suggests that IRA-B cells prevent sepsis by hastening the attack by neutrophils on pathogens, consequently allowing the immune system to shut down earlier. IRA-B cells normally hang out in the lining of the abdomen. But when they detect bacteria, they hustle to the spleen, where various kinds of immune cells mingle.

"They deliver a precise dose of GM-CSF where it is needed," Swirski says. A swift victory spurred by the chemical may be important, he says, because "the immune system is a double-edged sword in sepsis: it's needed to get rid of bacterial infection, but it can cause tremendous damage." For example, inflammation triggered by immune system cells might lead to the widespread blood clotting that afflicts many sepsis patients.

"It is quite a remarkable study, and quite surprising," Opal says. To move forward, he suggests, researchers should

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Still killing. Even with modern medical care, about a quarter of sepsis patients die.

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determine what range of pathogens the IRA-B cell works against and whether they can harness it to fight infections. Swirski and colleagues have already made one encouraging discovery, identifying IRA-B cells in people. In the future, the team suggests, it might be possible to grow the cells in culture and inject them into patients or to use drugs to spur their reproduction in the body.

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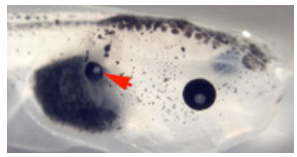
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