Treatment with lymph node cells controls dangerous sepsis in animal models

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An immune-regulating cell present in lymph nodes may be able to halt severe cases of sepsis, an out-of-control inflammatory response that can lead to organ failure and death. In the August 13 issue of *Science Translational Medicine*, a multi-institutional research team reports that treatment with fibroblastic reticular cells (FRCs) significantly improved survival in two mouse models of sepsis, even when delivered after the condition was well established. Even after treatment with antibiotics, sepsis remains a major cause of death.

"Our findings are important because, to our knowledge, no experimental therapeutic has shown such a significant survival benefit after the disease has progressed so far – in our study up to 16 hours after a sepsis -inducing injury," says Biju Parekkadan, PhD, of the Center for Engineering in Medicine at Massachusetts General Hospital (MGH), senior author of the *Science Translational Medicine* report. "The effectiveness of late treatment is essential because septic patients often do not receive treatment until hours or days after the original injury occurred."

Usually set off when bacteria or other infectious agents invade the bloodstream, sepsis involves an over-reaction of the immune system in which signaling molecules called cytokines attract excessive numbers of immune cells to the site of an infection or injury. Those cells secrete more cytokines, which recruit even more immune cells leading to a vicious cycle called a cytokine storm. Instead of stopping the initial infection, immune factors attack the body's tissues and organs, potentially leading to organ failure. Worldwide, more than 140,000 people die from sepsis each week.

Potential sepsis treatments targeting the activity of single molecules have not been successful, the authors note, probably because the condition involves complex interactions among many inflammatory pathways. Treatments using cells, however, can target the action of several molecules, influencing multiple disease pathways and potentially responding to changes in a patient's disease state. Since FRCs are known to regulate many aspects of the immune response within lymph nodes, the researchers investigated whether introducing FRCs to the site of a sepsis-inducing infection could modulate the inflammatory response.

The first experiments used two mouse models – one that uses a bacterial toxin associated with some forms of sepsis, the other in which an injury to the large intestine exposes the abdominal cavity to intestinal contents.

The researchers showed that infusing FRCs into the abdominal cavity significantly improved survival in both young and aged mice with toxin-induced sepsis. FRC administration also led to greatly increased survival in the intestinal injury model, which produces a more severe form of sepsis, even though both FRC-treated mice and saline-treated control animals also were treated with antibiotics.

Since the FRCs used in those experiments were cultured from the lymph nodes of the animals to which they were administered, the researchers repeated the experiments using FRCs cultured from an unrelated strain of mice. The increased survival of animals receiving FRCs – with 89 percent surviving versus 14 percent of those treated with saline – implied that cells from healthy human donors could be cultured, stored and used without the need to match immune or other factors in the recipients. The test of treatment delivered well after sepsis was established showed that FRCs delivered 16 hours after a sepsis-inducing injury – instead of 4 hours in the other experiments – also produced a significant survival advantage.

Experiments investigating the mechanism behind the treatment indicated that FRC administration prevented both damage to the spleen – which filters pathogens from the blood – and the death of several types of immune cells normally present in the organ. Preservation of spleen function probably explains the reduced levels of bacteria in the bloodstream of FRC-treated animals, even though bacterial levels in the abdominal cavity, where sepsis was induced and into which FRCs were infused, remained unchanged. Additional evidence suggested that activity of the signaling molecule nitric oxide may be essential to the effects of FRC treatment.

"The development of FRC therapy for testing in human patients is the critical path we plan to follow, and this study is a good first step," says Parekkadan, an assistant professor of Surgery at Harvard Medical

School.

More information: "Lymph node fibroblastic reticular cell transplants show robust therapeutic efficacy in high-mortality murine sepsis," by A.L. Fletcher et al. stm.sciencemag.org/lookup/doi/ … scitranslmed.3009377

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