**Novel Role for Spleen B Cells in Inflammatory Response to Bacterial Toxins**

Research team led by the University of Tsukuba identifies a role for spleen marginal zone B lymphocytes in intensifying the inflammatory response to endotoxins through cytokine production

Tsukuba, Japan – The inability to adequately respond to infection can cause a whole-body state of inflammation known as sepsis. This can eventually lead to systemic inflammatory response syndrome (SIRS), and even death. White blood cells known as B lymphocytes (B cells) produce antibodies in response to infections such as blood-borne pathogens. B cells of the marginal zone (MZ), which separates circulating blood from spleen lymphoid tissue, contribute to this early immune response, but their role in inflammation has remained unclear.

A research team centered at the University of Tsukuba has now revealed that MZ B cells also produce the signaling proteins cytokines and chemokines involved in inflammatory responses. They recently reported the results of their study in *Nature Communications*.

Lipopolysaccharides (LPS) are endotoxic products from Gram-negative bacteria that can trigger SIRS. The researchers showed that mice injected with LPS from *E. coli* were more resistant to endotoxic shock and lived longer if they lacked MZ B cells, suggesting these cells' crucial role in inflammatory response against LPS. MZ B cells were found to produce large quantities of the inflammatory cytokine interleukin (IL)-6, as well as some chemokines, in response to LPS stimulation.

The researchers experimented with blocking the IL-6 function slightly before or a few hours after the LPS injection. "We found that mice were protected against endotoxic shock and survived for longer if IL-6 signaling was stopped at the later stage," lead author Shin-ichiro Honda says. "This is significant in developing treatments for sepsis." After examining the signaling process in greater detail, another protein of the immune system, Toll-like receptor 4 (TLR4), was shown to be necessary for IL-6 production; LPS directly stimulates MZ B cells via TLR4, leading to the production.

Fcα/μR is mainly expressed on lymphoid tissue immune cells, where it acts as a receptor for IgA and IgM antibodies. It is also expressed on MZ B cells, but its role there was unknown. The researchers studied in Fcα/μR-deficient mice and found that their MZ B cells produced much less IL-6 in response to LPS than those of control mice. "We observed that a physical association with Fcα/μR was required for forming the TLR4 complex and IL-6 production in response to LPS," corresponding author Akira Shibuya explains. MZ B cells therefore emerge as a regulator of immune responses with a strong pro-inflammatory role in IL-6 production in endotoxic shock.

The article, "Marginal zone B cells exacerbate endotoxin shock via interleukin-6 secretion induced by Fcα/μR-coupled TLR4 signalling" was published in *Nature Communications* at DOI: 10.1038/ncomms11498

**Release Summary Text:** University of Tsukuba-led researchers have identified a new role for marginal zone B lymphocytes in enhancing inflammatory responses to bacterial lipopolysaccharides. Marginal zone B cells were shown to produce pro-inflammatory cytokine interleukin-6 in response to lipopolysaccharide stimulation. Interleukin-6 production requires TLR4 signaling in relation to the antibody receptor Fcα/μR. These findings broaden understanding of marginal zone B cell function and interleukin-6 signaling in the immune system, which could be exploited to treat sepsis.

**Primary Keywords:** Biology

**Additional Keywords:** Biochemistry, Cell Biology, Molecular Biology, Toxicology

**Twitter Comment:** Researchers identify new role for spleen B cells in sepsis

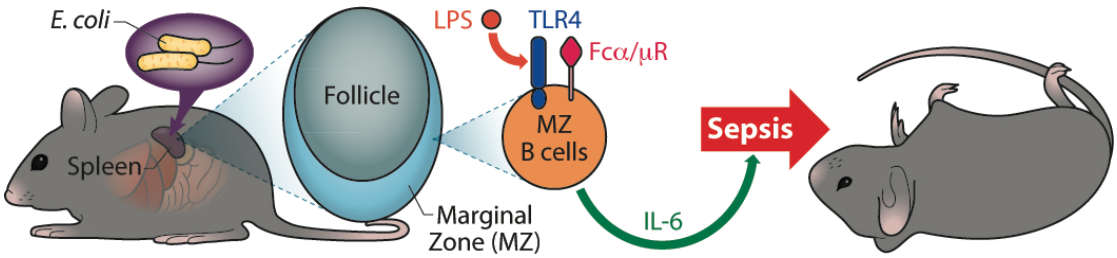


**Image Title:** Spleen MZ B cells contribute to inflammatory response against endotoxins

**Image Caption:** B cells from the marginal zone (MZ) of the spleen produce high levels of the pro-inflammatory cytokine interleukin-6 (IL-6) in response to bacterial endotoxins. This response is coordinated by a signaling reaction involving TLR4 and Fcα/μR, and leads to systemic inflammation and endotoxic shock.