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Novel role for spleen B cells in inflammatory response to bacterial toxins

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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.

More information: Shin-ichiro Honda et al. Marginal zone B cells exacerbate endotoxic shock via interleukin-6 secretion induced by Fcα/μR-coupled TLR4 signalling, *Nature Communications* (2016). DOI: 10.1038/ncomms11498

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