Frontline science: Endotoxin-induced immunotolerance is associated with loss of monocyte metabolic plasticity and reduction of oxidative burst.

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Abstract

Secondary infections are a major complication of sepsis and associated with a compromised immune state, called sepsis-induced immunoparalysis. Molecular mechanisms causing immunoparalysis remain unclear; however, changes in cellular metabolism of leukocytes have been linked to immunoparalysis. We investigated the relation of metabolic changes to antimicrobial monocyte functions in endotoxin-induced immunotolerance, as a model for sepsis-induced immunoparalysis. In this study, immunotolerance was induced in healthy males by intravenous endotoxin (2 ng/kg, derived from Escherichia coli O:113) administration. Before and after induction of immunotolerance, circulating CD14+ monocytes were isolated and assessed for antimicrobial

functions, including cytokine production, oxidative burst, and microbial (Candida albicans) killing capacity, as well metabolic responses to ex vivo stimulation. Next, the effects of altered cellular metabolism on monocyte functions were validated in vitro. Ex vivo lipopolysaccharide stimulation induced an extensive rewiring of metabolism in naive monocytes. In contrast, endotoxin-induced immunotolerant monocytes showed no metabolic plasticity, as they were unable to adapt their metabolism or mount cytokine and oxidative responses. Validation experiments showed that modulation of metabolic pathways, affected by immunotolerance, influenced monocyte cytokine production, oxidative burst, and microbial (C. albicans) killing in naive monocytes. Collectively, these data demonstrate that immunotolerant monocytes are characterized by a loss of metabolic plasticity and these metabolic defects impact antimicrobial monocyte immune functions. Further, these findings support that the changed cellular metabolism of immunotolerant monocytes might reveal novel therapeutic targets to reverse sepsis-induced immunoparalysis.

Involved units

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Leibniz-HKI-Authors



Mark Gresnigt

Details

Topics

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Immunology of Fungal Infections

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