Hyperresponsiveness of mice deficient in plasma-secreted sphingomyelinase reveals its pivotal role in early phase of host response.

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Abstract

Plasma secretion of acid sphingomyelinase is a hallmark of cellular stress response resulting in the formation of membrane embedded ceramide-enriched lipid rafts and the reorganization of receptor complexes. Consistently, decompartmentalization of ceramide formation from inert sphingomyelin has been associated with signaling events and regulation of the cellular phenotype. Herein, we addressed the question of whether the secretion of acid sphingomyelinase is involved in host response during sepsis. We found an exaggerated clinical course in mice genetically deficient in acid sphingomyelinase characterized by an increased bacterial burden, an increased phagocytotic activity, and a more pronounced cytokine storm. Moreover, on a functional level, leukocyte-endothelial interaction was found diminished in sphingomyelinase-deficient animals corresponding to a distinct leukocytes' phenotype with respect to rolling and sticking as well as expression of cellular surface proteins. We conclude that hydrolysis of membrane-embedded sphingomyelin, triggered by circulating sphingomyelinase, plays a pivotal role in the first line of defense against invading microorganisms. This function might be essential during the early phase of infection leading to an adaptive response of remote cells and tissues.

Identifier

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