Septic Shock Sera Containing Circulating Histones Induce Dendritic Cell–Regulated Necrosis in Fatal Septic Shock Patients

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Résumé en anglais	Objectives: Innate immune system alterations, including dendritic cell loss, have been reproducibly observed in patients with septic shock and correlated to adverse outcomes or nosocomial infections. The goal of this study is to better understand the mechanisms behind this observation in order to better assess septic shock pathogenesis.Design: Prospective, controlled experimental study. Setting: Research laboratory at an academic medical center. Subjects: The study enrolled 71 patients, 49 with septic shock and 22 with cardiogenic shock. Seventeen healthy controls served as reference. In vitro monocyte-derived dendritic cells were generated from healthy volunteers. Interventions: Sera were assessed for their ability to promote in vitro dendritic cell death through flow cytometry detection in each group of patients. The percentage of apoptotic or necrotic dendritic cells was evaluated by annexin-V and propidium iodide staining. Measurements and Main Results: We observed that only patients with septic shock and not patients with pure cardiogenic shock were characterized by a rapid and profound loss of circulating dendritic cells. In vitro analysis revealed that sera from patients with septic shock induced higher dendritic cell death compared to normal sera or cardiogenic shock ($p < 0.005$). Sera from surviving patients induced dendritic cell death through a caspase-dependent apoptotic pathway, whereas sera from nonsurviving patients induced dendritic cell-regulated necrosis. Dendritic cell necrosis was not due to necroptosis but was dependent of the presence of circulating histone. The toxicity of histones toward dendritic cell could be prevented by recombinant human activated protein C. Finally, we observed a direct correlation between the levels of circulating histones in patients and the ability of the sera to promote dendritic cell-regulated necrosis. Conclusions: The study demonstrates a differential mechanism of dendritic cell death in patients with septic shock that is dependent on the severity of the disease.
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