Toll-like receptor 2 activation by bacterial peptidoglycan-associated lipoprotein activates cardiomyocyte inflammation and contractile dysfunction.

OBJECTIVE: Although cardiac dysfunction plays an important role in the pathogenesis of sepsis, the mechanisms that underlie cardiac dysfunction in sepsis remain poorly understood. Bacterial peptidoglycan-associated lipoprotein (PAL), an outer-membrane protein of Gram-negative bacteria, was recently found to be released into the bloodstream in sepsis and to cause inflammation and death in mice. The present studies assessed the effects of PAL on cardiomyocyte function and its signal transduction in cardiomyocytes.

DESIGN: Randomized prospective animal study. SETTING: Research laboratory. SUBJECTS: Male C57BL/6 mice, B6; 129S-Tnfrsf1a(tm1Imx) Tnfrsf1b(tm1Imx)/J knockout mice, Toll-like receptor 2 (TLR2) knockout mice, and myeloid differentiation factor 88 (MyD88) knockout mice.

MEASUREMENTS AND RESULTS: Immunohistochemical staining and immunoblot analysis indicated that intravenously injected PAL bound to myocardium. Injection of PAL decreased cardiac function in vivo. Challenge with PAL altered cell shortening and Ca2+ transients in isolated mouse cardiomyocytes but not in cardiomyocytes isolated from TLR2 -/- and MyD88 -/- mice. Cytokine profiling arrays demonstrated that tumor necrosis factor-alpha
(TNFalpha), granulocyte colony-stimulating factor, and interferon-gamma-production were elevated in PAL-treated cardiomyocytes. Increased TNFalpha production was abolished in MyD88 -/- cardiomyocytes but restored by adenovirally mediated expression of MyD88. PAL did not affect cell shortening and Ca2+ cycling in cardiomyocytes obtained from mice deficient for TNFalpha receptor (TNFR) 1 and TNFR2 (TNFR1/2 -/-). CONCLUSION: Our data reveal that PAL uses the TLR2/MyD88 signaling cascade to induce cardiomyocyte dysfunction and inflammatory responses and that TNFalpha is a major mediator of PAL-induced dysfunction in cardiomyocytes. These studies suggest that circulating PAL and other TLR2 agonists may contribute to cardiac dysfunction in sepsis.

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