Interferon-γ-Driven iNOS: A Molecular Pathway to Terminal Shock in Arenavirus Hemorrhagic Fever

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Arenaviruses such as Lassa virus (LASV) cause hemorrhagic fever. Terminal shock is associated with a systemic cytokine storm, but the mechanisms are ill defined. Here we used HLA-A2-expressing mice infected with a monkey-pathogenic strain of lymphocytic choriomeningitis virus (LCMV-WE), a close relative of LASV, to investigate the pathophysiology of arenavirus hemorrhagic fever (AHF). AHF manifested as pleural effusions, edematous skin swelling, and serum albumin loss, culminating in hypovolemic shock. A characteristic cytokine storm included numerous pro-inflammatory cytokines and nitric oxide (NO) metabolites. Edema formation and terminal shock were abrogated in mice lacking inducible nitric oxide synthase (iNOS), although the cytokine storm persisted. iNOS was upregulated in the liver in a T cell- and interferon-γ (IFN-γ)-dependent fashion. Accordingly, blockade of IFN-γ or depletion of T cells repressed hepatic iNOS and prevented disease despite unchecked high-level viremia. We identify the IFN-γ-iNOS axis as an essential and potentially druggable molecular pathway to AHF-induced shock.

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