T cell-dependence of Lassa fever pathogenesis.

Lassa virus (LASV), the causative agent of Lassa fever (LF), is endemic in West Africa, accounting for substantial morbidity and mortality. In spite of ongoing research efforts, LF pathogenesis and mechanisms of LASV immune control remain poorly understood. While normal laboratory mice are resistant to LASV, we report that mice expressing humanized instead of murine MHC class I (MHC-I) failed to control LASV infection and develop severe LF. Infection of MHC-I knockout mice confirmed a key role for MHC-I-restricted T cell responses in controlling LASV. Intriguingly we found that T cell depletion in LASV-infected HHD mice prevented disease, irrespective of high-level viremia. Widespread activation of monocyte/macrophage lineage cells, manifest through inducible NO synthase expression, and elevated IL-12p40 serum levels indicated a systemic inflammatory condition. The absence of extensive monocyte/macrophage activation in T cell-depleted mice suggested that T cell responses contribute to deleterious innate inflammatory reactions and LF pathogenesis. Our observations in mice indicate a dual role for T cells, not only protecting from LASV, but also enhancing LF pathogenesis. The possibility of T cell-driven enhancement and immunopathogenesis should be given
consideration in future LF vaccine development.