

Fulminant LCMV-induced CNS inflammation involves a self-increasing cytokine-chemokine cascade

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Intracerebral inoculation of immunocompetent mice with lymphocytic choriomeningitis virus (LCMV) normally results in fatal CD8⁺ T cell mediated meningoencephalitis. However, in CXCL10 deficient mice the virus-induced CD8⁺ T cell accumulation in the neural parenchyma is impaired, and only 30-50% of the mice succumb to the infection. Similar results are obtained in mice deficient in the matching chemokine receptor, CXCR3. Together these findings point to a key role for CXCL10 in regulating the severity of the LCMV-induced inflammatory process.

For this reason we now address the mechanisms regulating the expression of CXCL10 in the CNS of LCMV-infected mice.

Using various gene targeted mice including mice deficient in type I or II interferon (IFN) receptors, and bone marrow chimeras expressing CXCL10 only in resident cells or in bone marrow derived cells, we analyzed the up-stream regulation as well as the cellular source of CXCL10.

We found that expression of CXCL10 initially depends on signalling through the type I IFN receptor, while late expression and up-regulation requires type II IFN produced by the recruited CD8⁺ T cells. Throughout the infection the producers of CXCL10 are exclusively resident cells of the CNS, and astrocytes are the dominant expressors in the neural parenchyma, not microglia or recruited bone marrow derived cell types. These results are consistent with a model suggesting a bidirectional interplay between resident cells of the CNS and the recruited virus-specific T cells with astrocytes as active participants in the local antiviral host response.