

Poster presentation

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CXCL10 and CXCR3 modulate morbidity and brain invasion by parasites and T-cells in an African Trypanosomiasis mouse model

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from Infectious diseases of the nervous system: pathogenesis and worldwide impact
Paris, France. 10–13 September 2008

Published: 23 September 2008

BMC Proceedings 2008, 2(Suppl 1):P1

This abstract is available from: <http://www.biomedcentral.com/1753-6561/2/S1/P1>

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Human African Trypanosomiasis (HAT) is caused by sub-species of the extracellular parasite *Trypanosoma brucei*. Treatment of the late meningoencephalitic stage of the disease still relies on very toxic drugs. For understanding morbidity and design of markers for better staging of HAT, studies on mechanisms by which the parasites pass across the blood-brain barrier (BBB) are important. We have previously observed that trypanosomes, similar to leukocytes, invade the brain by a multi-step process in *Trypanosoma brucei brucei*-infected mice. We here studied expression of chemokine transcripts in the brain using microarray and real-time PCR and related this to trafficking of trypanosomes and leukocytes across the BBB by immunohistochemistry and to morbidity in chemokine and chemokine receptor gene deleted mice. At 15 days post infection (p.i.), when parasites had first invaded the brain parenchyma, CXCL10 and CCL28 transcripts were differentially up-regulated in the brain compared to 6 days p.i. More chemokine transcripts, and especially CXCL9 and 10, were differentially expressed in the brains at 28 days p.i. Expression of these transcripts was significantly reduced in infected IFN-gamma^{-/-} mice, indicating an important role of this cytokine in their induction. Mice deficient of CXCL10 or its receptor, CXCR3, showed reduced accumulation of CD4⁺ and CD8⁺ T cells, and trypanosomes in the brain compared to WT mice, notwithstanding similar levels of parasitemia, and a compen-

satory up-regulation of transcripts for the other two CXCR3 ligands, CXCL9 and 11, in infected mice. A reduced weight occurring in infected WT mice was not observed in either CXCR3^{-/-} or CXCL10^{-/-} infected mice. These results suggest that CXCL10/CXCR3 interaction plays a crucial role in the recruitment of T-cells into the brain parenchyma and may modulate factors involved in trypanosome brain invasion, which leads to morbidity.

This work was supported by grants from the European Union (FP6-2004-INCO-DEV-3 032324)