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Trypanosoma brucei triggers its own multi-step entry into the brain

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Sleeping Sickness or Human African Trypanosomiasis (HAT), which is a fatal disease if left untreated, is caused by subspecies of the extracellular parasite, *Trypanosoma brucei (Tb)*, spread by the tsetse fly in sub-Saharan Africa. Two stages of the disease are recognized: Stage 1, in which the parasites appear in the hemolymphatic system and Stage 2, presented by severe signs of brain involvement. The diagnostic criteria for Stage 2 are under debate and rely on finding trypanosomes and/or an elevated number of white blood cells (WBC) in the cerebrospinal fluid. Patients in Stage 1 are treated with drugs with poor penetration of the blood-brain barrier (BBB), whereas arsenic compounds that permeate the BBB, but which can be lethal, are widely used for Stage 2 patients. Disclosing mechanisms by which the parasites spread from the blood vessels into the brain could contribute to develop biomarkers for better staging of the diseases and treatment.

Data obtained from studies of experimental rodent models of African trypanosomiasis will be presented, showing that invasion of the parasites into the brain is a multi-step process, similar to that of WBC, and regulated by host-derived molecules, which can be analyzed in body fluids. During early stage of infection, the rodent pathogenic *Tb brucei* parasites and WBC appear in the choroid plexus and the circumventricular organs that lack a BBB. Certain of the signs of hypothalamic dysfunctions in the disease may be related to release of inflammatory molecules in these organs. At a later stage, the parasites and WBC penetrate the BBB. Studies using minocycline, which impedes passage of WBC into the brain, and different strains of mice, have shown that loss of weight and death is related to brain invasion and not to the systemic infection of the trypanosomes.

During the infection, trypanosomes trigger release of interferon (IFN)-γ, which plays an important role to permit the trypanosomes to cross the parenchymal basement membranes of the BBB. Array studies show up-regulated expression of the IFN-γ-inducible chemokine CXCL10. Mice with deleted genes encoding this chemokine show less parasite neuroinvasion and weight loss, but no reduced level of parasitemia. IFN-γ affects also synaptic functions in neuronal circuits of the brain. The level of IFN-γ and CXCL10 in the cerebrospinal fluids correlates with severity of the disease in patients with HAT.

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