

The role of interleukin-10 and monocytic cells in liver pathogenicity during African trypanosome infection.

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Abstract

African trypanosomes are unicellular protozoan parasites that cause sleeping sickness in humans and nagana in domesticated cattle, diseases with a major health and economical impact on sub-Saharan Africa. Due to ingenious immune evasion mechanisms used by the parasite, a vaccine to protect humans and livestock at risk is currently lacking. Moreover, the trypanocidal drugs in use have a high level of toxicity and the development of drug resistant parasites is reported. Since some host-trypanosome combinations lead to a chronic infection without apparent pathological symptoms, as is the case for trypanosome infected African wildlife, a focus on the mechanisms involved in the induction and/or prevention of pathology might provide new innovative ways of treatment.

To unravel pathways that control the pathogenicity associated with infection, we study the immune response and tissue injury at the level of the liver which is the main site of parasite clearance. Using two independent models of African trypanosome infection, i.e. *T. brucei* and *T. congolense* infections in C57BL/6 mice, we show here that the anti-inflammatory cytokine IL-10 plays a crucial protective role during infection. IL-10 can limit pathogenicity by reducing the recruitment and activation of inflammatory monocytic cells in the liver, so-called classically activated monocytic cells (M1). As such, this includes CD11b+Ly6C⁺ cells that migrate from the bone marrow to the periphery in a CCR2 chemokine receptor-dependent way and are activated towards a phenotype of TNF and iNOS producing inflammatory dendritic cells (Tip-DCs). Tip-DCs, through their production of TNF and nitric oxide (NO), are shown to contribute to the development of liver injury. In addition to a role in limiting M1/Tip-DC activation, IL-10 can also induce the development of alternatively activated monocytic cells (M2) that have an anti-inflammatory character. In this respect, we have identified selenoprotein P as an IL-10 inducible M2-associated marker that protects host liver cells from apoptosis by reducing oxidative stress-induced liver injury, hereby prolonging the lifespan of trypanosome infected mice.

In conclusion, by studying liver monocytic cell M1/M2 activation and the role of IL-10, we have unravelled pathways that contribute to or limit infection-associated pathogenicity during experimental African trypanosome infection. These findings could be used in the development of novel anti-pathology treatments for parasitic infection or, more generally, in pathological situations where hepatic injury is involved.