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Human African trypanosomiasis (HAT), also known as sleeping sickness, is caused by unicellular flagellated protozoan parasites belonging to the *Trypanosoma* genus. These parasites can also infect cattle and cause *Nagana*. During the whole course of infection, these parasites stay extracellular, exposing them to immune attacks by antibodies and microbicidal compounds released by myeloid cells. However, African trypanosomes have developed mechanisms to escape the immune system, causing chronic infection. Moreover, the immune response elicited to counteract the parasite growth causes different degrees of tissue damage depending on the host-parasite combination. Both natural and experimental African trypanosomiasis lead to different degrees of disease severity. In the Cellular and Molecular Immunology (CMIM) research unit, we used *T. congolense* infection in C57Bl/6 mice as a model to unravel the mechanisms underlying the infection-associated pathogenicity, in particular liver damage.

This infection model is characterized by a first peak of parasitemia in the early stage of infection. Production of inflammatory compounds, such as TNF, NO and IFN- $\gamma$ , by myeloid cells and T cells is indispensable to control this first parasite peak and leads to resistance to the infection. However, when prolonged such immune response results into tissue damage, -especially in the liver that is the primary organ for parasite control, shortening the survival of the host. -Therefore, the host requires the development of a regulatory/anti-inflammatory immune response that -limits the pathogenic inflammatory response and induces so-called trypanotolerance of the host to the disease. Hereby, in *T. congolense* infected C57Bl/6 mice, the -anti-inflammatory cytokine IL-10 plays a crucial role by limiting the production of -inflammatory compounds and -consequently protects the host against tissue damage ensuring its prolonged survival.

CD11b<sup>+</sup> myeloid cells have been associated to both resistance and tolerance to *T. congolense* infection. Indeed, (M1-type) myeloid cells are major producers of TNF and NO, while anti-inflammatory (M2-type) myeloid cells have been suggested to be IL-10 producers. In this work, we focused to dissect the contribution of myeloid cells to the switch of an inflammatory immune response to a regulatory/anti-inflammatory

immune response during *T. congolense* -infection in C57Bl/6 mice and hereby to investigate the (i) phenotypical and functional -heterogeneity -within the CD11b<sup>+</sup> myeloid cells and (ii) their contribution to the M1- or M2-type immune -response - during *T. congolense* infection.

Our results show that during the early stage of African trypanosome infection, Ly6C<sup>+</sup> -monocytes are massively recruited to the liver and are the main producers of TNF and NO. In addition, these cells, together with macrophages, can capture and eliminate -trypanosomes from the bloodstream. Upon contact between the parasite and myeloid cells, trypanosome-derived adenylate cyclase can limit the production of TNF by the myeloid cells, avoiding complete elimination of the trypanosomes.

After the first peak of parasitemia, the Ly6C<sup>+</sup> monocyte population declines while a CD11b<sup>+</sup> Ly6C<sup>-</sup> -myeloid cell population mobilizes in the liver of infected mice. IL-10 derived from the latter cells limits the production of TNF by Ly6C<sup>+</sup> monocytes in part through the -induction of NF- $\kappa$ B p50 nuclear translocation and hereby decreased liver damage and hence increase tolerance to infection.

The CD11b<sup>+</sup> Ly6C<sup>-</sup> myeloid cell population was found to include two subsets, namely Ly6C<sup>-</sup> monocytes and macrophages. Although, Ly6C<sup>-</sup> monocytes exhibit a less pronounced M2-type gene -signature compared to macrophages, they can limit the TNF production by Ly6C<sup>+</sup> -monocytes through IL-10 secretion. In addition, they can promote the differentiation of Ly6C<sup>+</sup> monocytes to macrophages. By performing these functions, Ly6C<sup>-</sup> -monocytes play a hepatoprotective role during *T. congolense* infection. Further investigation is - necessary to understand the contribution of macrophages in the outcome of infection.

With this work, we managed to unravel some pieces of the mechanism underlying the switch from a pro-inflammatory to a regulatory immune response during *T. congolense* -infection. These could be some of the flagstones that pave the long way for the development of -strategies -preventing infection-associated pathogenicity in

African trypanosomiasis, but also for -preventing pathogenicity associated with chronic liver inflammation in a more general way.