IL-27 IN AFRICAN TRYPANOSOMES: A DOUBLE-EDGED SWORD IN PARASITE CONTROL.

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African trypanosomiasis (AT), caused by extracellular protozoan parasites of the genus *Trypanosoma*, is a neglected tropical disease affecting both humans and livestock. Left untreated, the disease is characterized by a chronic inflammatory response, often lethal for the host. Like in most infectious diseases, the host's immune system balances mounting an efficient immune response and limiting collateral damage. While the anti-inflammatory IL-10 cytokine is paramount in limiting the AT-associated immunopathologies, interest has increased in IL-27 as another key immunomodulating cytokine.

An initial study showed that abrogation of the IL-27 receptor (IL-27R) results in an increased mortality due to uncontrolled IFN-γ production by $CD4^+$ Th1 cells and accumulation of TNF/iNOS producing dendritic cells (TIP-DCs) in the liver. To investigate the role of IL-27 in tsetse-transmitted AT, our research relied on pharmacological and genetic models, including α-IL-27 antibody-induced neutralization and genetic IL-$27^{-/-}$ mice. Ten days after inoculation by the bites *Glossina morsitans* flies, trypanosome counts in peripheral blood and bio-luminescent imaging revealed significantly better parasitaemia control in the absence of IL-27, which contrasts previous observations in IL-$27R^{-/-}$ mice infected through an intraperitoneal route. Using IL-27 reporter mice, the immunological response was studied in skin exposed to the infectious bites, showing a strong influx of myeloid cells and $CD4^+$ T lymphocytes, with myeloid cells such as inflammatory monocytes and neutrophils representing the main sources of IL-27. Myeloid cells were also identified as the principle early producers of IL-27 in the blood, liver and spleen. Mortality occurred earlier in IL-27 depleted mice, associated with elevated IFN-γ, MCP-1 and TNF-α plasma levels from day 7 post-infection onwards, without affecting IL-10 levels.

Altogether, our data show that myeloid cell-derived IL-27 plays an essential role in the control of inflammation during tsetse transmitted AT, limiting host immunopathology at the expense of increased systemic parasite establishment.