

Abstract:

During natural as well as experimental African trypanosomiasis, a range of severity of disease patterns is associated with different host-trypanosome combinations. As compared to *Trypanosoma congolense*, *Trypanosoma brucei* causes a pathogenic infection in C57BL/6 mice associated with important tissue damage, increased anemia burden and decreased survival. The increased pathogenicity in *T. brucei* infected mice correlated with uncontrolled IFN- γ production, marginal IL-10 production and continuous stimulation of classically activated monocyctic cells (M1), producing the pathogenic molecules TNF- α and NO. Conversely, the decreased pathogenicity of *T. congolense* infected mice was associated with induction of IL-10 production coinciding with the down-regulation of the IFN- γ response and M1 de-activation. The mechanisms implicated in this differential regulation of the immune response in *T. congolense* and *T. brucei* infected mice had not been identified. Our results show that naturally occurring CD4⁺Foxp3⁺ Tregs expanded in the spleen and the liver of *T. congolense* infected C57BL/6 mice. These cells produced IL-10, limited the production of IFN- γ by CD4⁺ and CD8⁺ effector T cells and down-regulated the activation M1 cells, resulting in reduced TNF- α production. Treg-mediated suppression did not hamper parasite clearance but was beneficial for the host survival by limiting the tissue damage.

Based on these results and on the observation that Tregs did not expand in *T. brucei* infected mice, we have assessed whether experimental expansion of Tregs could decrease pathogenicity of the disease in trypanosusceptible mice. CD28 superagonist antibody treatment mediated expansion of IL-10 producing Tregs, down-regulated IFN- γ production by T cells as well as TNF- α production by M1 cells, triggered the development of alternatively activated monocyctic cells (M2), delayed the onset of liver injury, diminished the anemia burden and prolonged the survival of *T. brucei* infected mice. However, the CD28 superagonist treatment revealed ineffective when delivered therapeutically to chronically infected mice. Therefore, we employed another modality to increase IL-10 levels during *T. brucei* infection, namely by delivering IL-10 using an adeno-associated viral vector (AAV). This treatment suppressed IFN- γ production, diminished TNF- α production by M1 cells, induced M2 activation and reduced the pathogenicity of the disease. Together, these data indicated that expansion of Tregs (through CD28 superagonist treatment) or delivery of IL-10 (through AAV treatment) could restore the balance between pro- and anti-inflammatory signals and hereby limit the pathogenicity of African trypanosomiasis.

Having shown that the CD28 superagonist and the IL-10-AAV treatment in *T. brucei* infected mice limited the production of the pathogenic compounds TNF- α and NO by M1 cells and induced M2 activation, we thought interesting to scrutinize the phenotype of monocyctic cells in *T. brucei* infected C57BL/6 mice. We show that CD11b⁺Ly6c⁺CD11c⁻ Monocytes gradually accumulated in the spleen, the liver and the lymph nodes of *T. brucei* infected mice and differentiated to CD11b⁺Ly6c⁺CD11c⁺ TIP-DCs, producing elevated levels of TNF- α and iNOS. In addition, the CD28 superagonist and the IL-10-AAV treatment limited the differentiation of Monocytes to TIP-DCs, hereby inhibiting their production of TNF- α and NO during infection. In addition, Monocytes from IL-10-AAV and CD28 superagonist treated infected mice were found to exhibit a M2 activation state. Hence, we have identified TIP-DCs as a major subset of pathogenic M1 cells during African trypanosomiasis infection and could demonstrate that Tregs and IL-10 can efficiently control the differentiation of Monocytes to TIP-DCs, protecting the host from TIP-DC mediated collateral tissue damage. IL-10-triggered Monocytes on the other hand likely represent a subset of M2 cells with potential anti-pathogenic activity.

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