Cellular dynamics of immune evasion during *Leishmania major* infection

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Infection by *Leishmania major* causes a severe disease and results in disfiguring skin lesions. There is no effective treatment or vaccine. While strong effector T cell responses are generated to infection, clearance of parasites is incomplete, and parasites survive indefinitely. The gap in knowledge is the cellular mechanisms that allow for the persistent infections to be established. Regulatory T cells (Tregs) are an essential part of the immune system, as they maintain peripheral tolerance and prevent autoimmunity, and they are not implicated in responding or recognizing foreign invaders. Curiously, 50% of all T cells in the healed lesions of patients are Tregs. We hypothesize that *L. major*-driven induction of the immunosuppressive microenvironment through recruitment of Tregs at the site of infection prevents parasite clearance.

To address this, we combined both *in vitro* and *in vivo* approaches employing a novel TCR transgenic mouse model, in which all T cell are able to recognize *L. major*. Using Intravital Multiphoton microscopy, we visually tracked *Leishmania*-specific T cell responses directly in the skin of live mice. These recordings show a significant recruitment of adoptively transferred effector T cells to the lesion site *in vivo*, displaying cellular behaviors consistent with antigen recognition at early and late stages of infection, yet cellular dynamics are augmented at the chronic stage, indicating a fundamentally altered environment. We show a large proportion of Tregs to be *L. major*-specific and *L. major*-specific Tregs are significantly more suppressive. Upon secondary distal challenge with killed *L. major*, Tregs rapidly expand at the original site of infection. Disturbing the effector T cell: Treg balance led to induction of parasite tolerance, suppression of anti-*Leishmania* effector responses and expansion of the lesion. Collectively, our findings show for the first time that parasite-specific Tregs influence effector T cell responses.

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