Investigating the roles of the cell regulator TRIM24 during visceral leishmaniasis

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Visceral leishmaniasis (VL) is a neglected tropical disease caused by infection with protozoan parasites *Leishmania donovani* and *L. infantum*. More than 95% cases of VL are fatal if left untreated, and current treatments are limited, expensive, and toxic, and there are currently no vaccines available. Macrophages are essential for the pathogenesis of VL, as *Leishmania* parasites modulate signalling pathways within macrophages to switch off their anti-parasite phenotypes, thereby avoiding their destruction while persisting in this niche. However, the mechanisms by which this occurs remain poorly understood. Recently TRIM24, a member of the tripartite motif protein family and a previously identified regulator of interferon STAT signalling, was predicted to be differentially expressed during VL. In this study we investigate the immune roles of TRIM24 in the steady state and during *L. donovani* infection by utilising TRIM24 knockout (KO) C57BL/6 mice. Immune characterisation of KO mice revealed TRIM24 to be dispensable for immune cell development *in vivo*, however generation of 50:50 mixed bone marrow chimeric mice led to a significant skew in favour of KO cells most notably in the bone marrow. Neutrophils, monocytes, macrophages, and B cells (but notably not T cells) were responsible for this selective advantage of KO cells, pointing to an interesting advantage specific to the bone marrow chimera system. *L. donovani* infection of bone marrow chimeras had little effect on this skew, and flow cytometry-based analysis of immune cells revealed little change in the release of the cytokines TNF, IFN-γ, IL-6 and IL-10 from T cells and macrophages/monocytes. This was reflected in *in vitro* studies using bone marrow-derived macrophages (BMMs), where loss of TRIM24 did not affect release of TNF or IL-6. However, an increase in iNOS+ cells and release of nitric oxide (a pro-inflammatory mediator important for macrophage-mediated parasite clearance) was observed from KO BMMs. Furthermore, these BMMs released more interferon-beta, providing a potential mechanism for increased iNOS expression. Interestingly, no change in *Leishmania* parasite burden was seen between infected WT and KO mice. Further transcriptomic analysis on BMMs infected *in vitro*, and bone marrow from chimeric and total WT and KO mice will provide a deeper understanding of the roles of TRIM24 during *L. donovani* infection.