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Leishmania inhibits antigen crosspresentation by direct cleavage of the SNARE VAMP8

Phagosomes play a key role in immunity by killing microbes and processing their antigens for T cell activation. Some intracellular pathogens such as *Leishmania* inhibit these steps and prevent phagosome maturation through different mechanisms. In the present study, we investigated the impact of infection on SNAREs (soluble *N*-ethylmaleimide-sensitive-factor attachment protein receptor) proteins involved in the trafficking to and from the phagosome. We discovered that upon infection, VAMP8, VAMP3, SNAP23, and syntaxin-4 were cleaved by GPI-anchored zinc metalloprotease GP63. Using a *L. major* gp63-KO mutant, we showed that this parasite protease is responsible for the cleavage of VAMP8 and other SNAREs in infected macrophages. We also found that *Leishmania* promastigotes inhibit antigen crosspresentation in a GP63-dependent manner. Using cells from VAMP8-deficient mice, we confirmed that this SNARE protein is required for antigen crosspresentation. Also, the phagosomal exclusion of Sec22b, one of the regulators in phagosome maturation and antigen cross presentation, was observed upon infection with *L. major* WT and gp63-KO add-back. Thus, we uncovered the existence of a novel mechanism used by *Leishmania* promastigotes to evade recognition by the immune system, whereby the parasites impair crosspresentation by degrading key regulators of vesicular trafficking.