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Alteration of the autophagic response by *Leishmania major* promastigotes

The protozoan parasite *Leishmania* causes a spectrum of diseases in humans, ranging from self-healing skin ulcers to life-threatening visceral infection. These parasites primarily infect macrophages and are renowned for their ability to sabotage host-cell signal transduction pathways. The Akt/mammalian Target Of Rapamycin (mTOR) axis plays a pivotal role in the regulation of multiple cellular processes, including protein synthesis, cytokine secretion, apoptosis, and autophagy. It is therefore a major target of infectious pathogens. In this study, we aimed to investigate the impact of *L. major* promastigotes on the Ak/mTOR axis and downstream autophagy-related events. Infection of bone marrow-derived macrophages with *L. major* promastigotes caused rapid, time-dependent degradation of key components of the Akt/mTOR signaling axis, including Akt, mTOR and the Tuberous Sclerosis Complex-2 (TSC-2). Disruption of this pathway by *L. major* was dependent on the GPI-anchored zinc-dependent metalloprotease GP63, an important virulence factor of this parasite. Interestingly, recruitment of the autophagic marker LC3 to the parasitophorous vacuole of *L. major* promastigotes was inhibited by GP63, possibly due to GP63-mediated cleavage of vesicle-associated membrane protein 8 (VAMP8). Indeed, absence of VAMP8 resulted in inhibition of LC3 recruitment to phagosomes containing GP63-deficient parasites. This study highlights a novel pathogenic mechanism used by *L. major* to interfere with the autophagic response and will provide a better understanding of *Leishmania* pathogenesis. *Supported by CIHR*