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Synaptotagmin XI, a negative regulator of cytokine secretion and phagocytosis, is targeted by GP63

Leishmania parasites infect phagocytic cells, especially macrophages. An important pathogenesis factor in *Leishmania* is the GP63 metalloprotease. GP63 alters multiple modules of macrophage signalling and cleaves components of the vesicle fusion machinery, ensuing in weakened antimicrobicidal responses. Synaptotagmins (Syts) are membrane proteins that regulate vesicle docking and fusion in processes such as exocytosis and phagocytosis. Syts possess a transmembrane domain, and two conserved tandem Ca^{2+}-binding C2 domains. However, Syts IV and XI possess a conserved serine in their C2A domain that precludes these Syts from binding Ca^{2+}, and from mediating vesicle fusion. Given the importance of vesicular trafficking in macrophages, the objective of this research was to elucidate the role of Syt XI in cytokine secretion and phagocytosis, and to investigate the impact of GP63 on Syt XI function. We demonstrated that Syt is expressed in macrophages, localized in transferrin receptor 1-containing recycling endosomes, and recruited to early phagosomes. Syt XI had a direct effect on the secretion of tumour necrosis factor (TNF) and interleukin 6 (IL-6), and on phagocytosis. Whereas siRNA-mediated knockdown of Syt XI potentiated secretion of these cytokines and particle uptake, overexpression of a Syt XI construct suppressed these processes. On the other hand, Syt XI was not recruited to phagosomes containing *L. major* promastigotes expressing GP63. Upon finding that GP63 caused Syt XI degradation and augmented the release of TNF and IL-6, we showed that secretion of these cytokines depended on Syt XI degradation. Altogether, our data reveal novel roles for Syt XI, and provide a mechanism by which *Leishmania* induces the secretion of proinflammatory cytokines.