Title:	A novel leishmanial copper P-type ATPase plays a vital role in parasite infection and intracellular survival
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Abstract:	Copper (Cu) is essential for all life forms; however, in excess, it becomes toxic. Toxic properties of Cu are known to be utilized by host species against various pathogenic invasions. Leishmania, in both free-living and intracellular forms, exhibits appreciable tolerance toward Cu stress. While determining the mechanism of Cu-stress evasion employed by Leishmania, we identified and characterized a hitherto unknown Cu-ATPase in Leishmania major and established its role in parasite survival in host macrophages. This novel L. major Cu-ATPase, LmATP7, exhibits homology with its orthologs at multiple motifs. In promastigotes, LmATP7 primarily localized at the plasma membrane. We also show that LmATP7 exhibits Cu-dependent expression patterns and complements Cu transport in a Cu-ATPase-deficient yeast strain. Promastigotes overexpressing LmATP7 exhibited higher survival upon Cu stress, indicating efficacious Cu export compared with Wt and heterozygous LmATP7 knockout parasites. We further explored macrophage–Leishmania interactions with respect to Cu stress. We found that Leishmania infection triggers upregulation of major mammalian Cu exporter, ATP7A, in macrophages, and trafficking of ATP7A from the trans-Golgi network to endolysosomes in macrophages harboring amastigotes. Simultaneously, in Leishmania, we observed a multifold increase in LmATP7 transcripts as the promastigote becomes established in macrophages and morphs to the amastigote form. Finally, overexpressing LmATP7 in parasites increases amastigote survivability within macrophages, whereas knocking it down reduces survivability drastically. Mice injected in their footpads with an LmATP7-overexpressing strain showed significantly larger lesions and higher amastigote loads as compared with controls and knockouts. These data establish the role of LmATP7 in parasite infectivity and intramacrophagic survivability.
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