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Molecular Characterization of Arginine Sensing Response in Unravelling Host-Pathogen Interactions in Leishmania

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Abstract : The extensive interaction between the host and pathogen metabolic networks decidedly shapes the outcome of infection. Utilization of arginine by the host and pathogen is critical for determining the outcome of pathogenic infection. Infections with L. donovani, an intracellular parasite, will lead to an extensive competition of arginine between the host and the parasite donovani infection. One of the major amino acid (AA) sensing signaling pathways in mammalian cells are the mammalian target of rapamycin complex I (mTORC1) pathway. mTORC1, as a sensor of nutrient, controls numerous metabolic pathways. Arginine is critical for mTORC1 activation. SLC38A9 is the arginine sensor for the mTORC1, being activated during arginine sufficiency. L. donovani transport arginine via a high-affinity transporter (LdAAP3) that is rapidly up-regulated by arginine deficiency response (ADR) in intracellular amastigotes. This study, to author's best knowledge, investigates the interaction between two arginine sensing systems that act in the same compartment, the lysosome. One is important for macrophage defense, and the other is essential for pathogen virulence. We hypothesize that the latter modulates lysosome arginine to prevent host defense response. The work presented here identifies an upstream regulatory role of LdAAP3 in regulating the expression of SLC38A9-mTORC1 pathway, and consequently, their function in L. donovani infected THP-1 cells cultured in 0.1 mM and 1.5 mM arginine. It was found that in physiological levels of arginine (0.1 mM), infecting THP-1 with Leishmania leads to increased levels of SLC38A9 and mTORC1 via an increase in the expression of RagA. However, the reversal was observed with LdAAP3 mutants, reflecting the positive regulatory role of LdAAP3 on the host SLC38A9. At the molecular level, upon infection, mTORC1 and RagA were found to be activated at the surface of phagolysosomes which was found to form a complex with phagolysosomal localized SLC38A9. To reveal the relevance of SLC38A9 under physiological levels of arginine, endogenous SLC38A9 was depleted and a substantial reduction in the expression of host mTORC1, its downstream active substrate, p-P70S6K1 and parasite LdAAP3, was observed, thereby showing that silencing SLC38A9 suppresses ADR. In brief, to author's best knowledge, these results reveal an upstream regulatory role of LdAAP3 in manipulating SLC38A9 arginine sensing in host macrophages. Our study indicates that intra-macrophage survival of L. donovani depends on the availability and transport of extracellular arginine. An understanding of the sensing pathway of both parasite and host will open a new perspective on the molecular mechanism of host-parasite interaction and consequently, as a treatment for Leishmaniasis.

Keywords : arginine sensing, LdAAP3, L. donovani, mTORC1, SLC38A9, THP-1
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