HEMOGLOBIN ENDOCYTOSIS AND TRAFFICKING TO THE LYSOSOMES: A NOVEL PROCESS TO GENERATE INTRACELLULAR HEME BY LEISHMANIA FOR THEIR SURVIVAL

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Leishmania lack a complete heme biosynthetic pathway and must acquire heme from extracellular source. However, the process by which *Leishmania* acquire heme from the host is not well known. Previously, we have shown that a hexokinase localized in the flagellar pocket of *Leishmania* mediated hemoglobin (Hb) endocytosis (*J. Biol. Chem.* 1989; *J. Biol. Chem.* 2005). However, how Hb is degraded to generate intracellular heme is not known. To understand the regulation of Hb trafficking in *Leishmania*, we have cloned, expressed and characterized the function of two endocytic GTPase namely, Rab5 and Rab7 from *Leishmania*. We have found that Rab5 in *Leishmania*, localize in early endocytic compartment, regulate early steps of Hb endocytosis (*EMBO J. 2003*) and Rab7 mediates the transport of internalized Hb to the lysosomes. Subsequently, we have overexpressed Rab7 and its mutants in *Leishmania* as GFP fusion proteins to determine the role of Rab7 in Hb trafficking. Kinetics analysis of Hb trafficking reveals that targeting of Hb to the late compartment is much faster in Rab7:WT and Rab7:Q66L (GTP locked) overexpreesed cells than control *Leishmania*. Interestingly, cells overexpressing GDP locked negative mutant (Rab7:T21N) inhibit transport of internalized Hb to the lysosomes and these cells grow at a much slower rate than wild type *Leishmania*. However, Rab7:T21N overexpressed cells grow almost like the control cells by the addition of exogenous heme suggesting that Rab7 in GTP form is required to target Hb to the lysosomes to generate intracellular heme.

Key words: *Leishmania*, Hemoglobin, Endocytosis