Abstract

Requirement of iron for a wide range of organisms as an essential micronutrient is very well documented. Survival and virulence of any pathogen is crucially dependent on the availability of iron. Upon infection of mammalian host by *Mycobacterium tuberculosis (M.tb)*, there ensues a tussle between the invading pathogen on one side versus the host cells for control of iron supplies. Despite the host iron regulatory mechanisms intracellular *M.tb* is able to continue accumulation of iron, this suggests the existence of some unknown iron acquisition pathways operating in macrophage infected with *M.tb*. Our current investigation explores the role of a secreted form of the mammalian moonlighting protein glyceraldehyde-3-phosphate dehydrogenase (sGAPDH) which is hijacked to traffic iron carrier proteins into *M.tb* infected cells. Utilizing a combination of cell biological, biochemical and microscopy based tools our studies reveal that there is an enhanced uptake of iron replete lactoferrin into *M.tb* infected macrophage cells mediated by sGAPDH. Further our results also reveal that sGAPDH dependent lactoferrin trafficking is taking place at subcellular compartment where we observed *M.tb* containing phagosomes are in direct contact with internalized lactoferrin and sGAPDH containing vesicles. Once this iron carrier protein reaches to the phagosome, intraphagosomal *M.tb* can utilize this iron through its iron chelating molecules siderophores. Recent report suggests that *M.tb* can acquire iron by cell surface sequestration and internalization of human holo transferrin and lactoferrin. Our current study also illustrates a siderophore independent pathway in which intracellular *M.tb* utilizes host sGAPDH for direct internalization of lactoferrin. Overall our findings establish a role for the evolutionary conserved molecule GAPDH in delivery of iron carrier protein lactoferrin into *M.tb* infected macrophage and intraphagosomal *M.tb*. This study uncovers a hitherto unknown pathway of mammalian iron acquisition which is hijacked by intraphagosomal *M.tb* to access extracellular host iron sources. These findings identify a novel target for the regulation of pathogenesis of *M.tb*.