Comparative Proteomics to Define Adaptations to Purine Stress in *Leishmania*

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Abstract

Leishmania are protozoan parasites that cause significant morbidity and mortality in humans, afflicting approximately 12 million people worldwide. These parasites are auxotrophic for purines and have evolved a unique set of purine transporters and salvage enzymes to scavenge these essential nutrients from their host. Hence, purine salvage components provide attractive targets for drug design. An ability to adapt to changes in the purine milieu is vital for *Leishmania* to survive in their host. Withdrawal of extracellular purines leads to an acute increase in key purine transporters and salvage enzymes. This augmentation is not due to an increase in mRNA abundance or stability. *Since regulation is post-transcriptional, it is our goal to use proteomic methods to provide insight into the cellular networks and pathways involved in this adaptation to purine stress.* Two strategies are proposed. First, to quantify the temporal changes in the *Leishmania donovani* proteome upon purine-starvation, an accurate mass and time (AMT) tag strategy is delineated. A broad AMT database will be constructed from parasites grown under purine-free and purine-replete conditions and used to facilitate high-throughput accurate measurements on relative protein abundance between purine-starved and purine-replete parasites. Second, since it is conjectured that part of the response to purine stress involves the post-translational modification of regulatory proteins, the phosphoproteome of purine-starved and purine-replete *L. donovani* will be compared. It is anticipated that these studies will be of broad impact, illuminating the means by which *Leishmania* adapt to changes in their host purine environment and likely providing novel targets and pathways for future therapeutic exploration.