Mistargeting of aggregation-prone mitochondrial proteins activates a nucleus-mediated posttranscriptional quality control pathway in trypanosomes

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Mitochondrial quality control (MQC) is the network of pathways by which eukaryotic cells monitor and maintain the function of their mitochondria. *Trypanosoma brucei* has a large single mitochondrion, which prevents the elimination of dysfunctional mitochondria as in some other organisms. When this essential mitochondrion is not functioning correctly, for example when mitochondrial protein import is defective, cell viability suffers. The processes by which this parasite regulates its mitochondrial function are of great interest, particularly in relation to its life cycle, where the mitochondrion undergoes massive programmed morphological and functional alterations.

MQC pathways in yeast and metazoa are regulated on the transcriptional level. However, in *T. brucei*, due to polycistronic transcription, MQC regulation in this way is not possible. Additionally, other than ubiquitin and the proteasome, orthologues of most common MQC factors found in yeast and metazoa are absent in *T. brucei.* Mitochondrial biogenesis in *T. brucei* has been shown to be greatly impacted by convergent evolution, and we expect the same to be the case for mechanisms governing MQC.

95% of mitochondrial proteins in *T. brucei* are encoded in the nuclear DNA. The multisubunit ATOM complex is the mediator of protein import through the mitochondrial outer membrane in trypanosomes (Pusnik et al., 2011, Mani et al., 2015). We show data demonstrating the existence of a MQC pathway in *T. brucei* triggered when import of aggregation-prone proteins is blocked, specifically. Using a variety of proteomic and biochemical approaches, we show that the proteasome and putative components of a ubiquitin-driven pathway are recruited to the mitochondrion upon the induction of this import defect. Trypanosomatid-specific candidates were investigated as to their roles within this MQC pathway. Of particular interest is a nuclearly-localised protein with a ubiquitin-like domain which is released into the cytoplasm upon the induction of a mitochondrial import defect. Nuclear release of this protein is required for this MQC mechanism to function.