REGULATING THE TRANS-REGULATORS: INVESTIGATING THE PRMT7 MOLECULAR PATHWAY AS AN EPIGENETIC REGULATOR OF LEISHMANIA VIRULENCE

PRINCIPAL INVESTIGATORS

ANGELA KAYSEL CRUZ
Ribeirão Preto School of Medicine / University of São Paulo (USP)

PEGINE WALRAD
University of York

ABOUT THE PROJECT

FAPESP Process 2015/13618-8
Term: Apr 2016 to Mar 2019
Thematic Project
UKRI – MRC (Newton Fund)

CONTACT

✉ akcruz@fmrp.usp.br

Species of Leishmania threaten 350 million people worldwide on four continents. New treatments and vaccines are desperately needed and the UK and Brazilian governments are committed to the World Health Organization's recent call to further support Neglected Tropical Disease research. The single-cell Leishmania parasite differentiates in distinct forms during its lifecycle to adapt to different hosts; moving from mammals to sandflies and back to mammals by sandfly bites. Major changes to the parasite's morphology, metabolism and virulence proteins occur during these transitions that enable them to survive. Leishmania gene expression relies almost exclusively upon mRNA regulation. In response to changes in the environment, specific parasite proteins bind mRNAs and target them for protein production to guide and promote adaptation. Proteins that control the adaptation of these parasites enable them to survive in and infect humans. Such proteins are essential for the virulence and spread of the Leishmania parasite infection. We have recently isolated a major control panel "Regulator" protein, PRMT7, which controls Leishmania parasite virulence in mammalian infections. Very few Leishmania regulator proteins have yet been identified and this finding represents a major leap forward to isolate and examine this regulatory pathway and interfering with parasite virulence. To study the PRMT7 regulation pathway and identify the way this protein functions, we have assembled a team of experts in Leishmania parasite PRMT proteins, RNA regulators and protein interactions. We believe insight into this pathway may help to understand some parasite resources to successfully establish human infections. We have identified some downstream target proteins of PRMT7 and now seek to determine if they are regulated by PRMT7 and whether they participate in Leishmania parasite virulence. These Leishmania proteins are different from human proteins; therefore we can use these differences to target Leishmania-specific virulence factors, block their function and block Leishmaniasis from developing. Significant findings may provide insight to Leishmaniasis research. We propose to find more regulators of Leishmania virulence using the PRMT7 virulence pathway. We will identify how these regulators function, and test whether any are essential for parasite survival. The novelty and importance of our project is four fold: 1. PRMT7 is the only Protein aRginine Methyl Transferase enzyme that has been characterized in Leishmania parasites thus far and we demonstrated an inverse correlation between the protein level and virulence (Ferreira et al., 2014). 2. Methylation as a protein modification is uncharacterised in *Leishmania spp.* parasites. 3. Regulatory RNA binding proteins (RBPs) that are important in parasite lifecycle differentiation, human infectivity and virulence are largely unknown in Leishmania. 4. The 3-dimensional molecular structures of RBPs and mRNA: protein complexes are largely unknown in all parasites and are absent in Leishmania.