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Toxoplasmic eye disease: Unraveling the role of the arginine methyltransferase 1 (PRMT1) during Toxoplasma infection

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Toxoplasmosis is a devastating disease. It is the most common infection of the retina, causing loss of sight. This parasite is life threatening and damages eye and brain when it infects a fetus in utero before the immune system is mature, if untreated. Almost all such children have damage at birth or to their eyes by the time they are teenagers and many are reported to have cognitive impairment and some develop seizures or motor abnormalities secondary to infection by early adolescence. The proposal study will highlight the role of the arginine methyl transferase in gene expression and cell cycle regulation in Toxoplasma gondii.

The arginine methyl transferase family (PRMT) has been implicated in a variety of cellular processes including signal transduction, epigenetic regulation and DNA repair pathways in many organisms. PRMT1 and PRMT4 are thought to be the most relevant enzymes from this family and responsible for the majority of PRMT activity in Toxoplasma. They have been reported to act upon histones H4 and H3, respectively, and this activity has been correlated with transcription of bradyzoite specific genes and stage conversion between tachyzoites and bradyzoites. In this study, we have generated T. gondii mutants lacking TgPRMT1, Tgprmt1Δ. The deletion of PRMT1 gene in T. gondii RH hxgprt-strain was carried out by double homologous recombination using a PCR generated disruption cassette which contains the selectable marker hypoxanthine-xanthine-guanine phosphoribosyltransferase (HXGPRT). Tgprmt1Δ parasites exhibit morphological defects during cell division and grow slowly, and this phenotype was reversed in a complemented strain. We mapped PRMT1 histone methylation using mass spectrometry techniques on wild type, knockout, and complemented parasites. Surprisingly the proposed substrate of TgPRMT1, R3 of histone 4, was not methylated in any of the 3 strains. Interestingly, we found an increase in monomethylation of histone 3 in Tgprmt1Δ, which was not present in the wild-type or complemented strain. This finding was accompanied by an increase in steady-state mRNA levels of PRMT2, 3, 4 and 5. Whole genome expression profiling was performed, illustrating differences in gene expression in Tgprmt1Δ relative to the complemented and wild-type strains. In summary, the current study provides genetic evidence for the role of TgPRMT1 in gene expression and cell cycle regulation of the parasite.

Biography

Kamal El Bissati received his Ph.D. from the University of Pierre and Marie Curie and Ecole Normale Superieure, Ulm, Paris. He was a postdoctoral fellow at the University of Connecticut Medical School from 2003-2008. His pioneering work has led to develop live attenuated strains for malaria vaccination. Then, he expends his scientific career at Albert Einstein College of Medicine in New York where he was appointed as Instructor in the Department of Pathology. He is currently Research Assistant Professor in the Department of Ophthalmology and Visual Sciences at the University of Chicago Medical Center. His major research interests aim to decipher novel ways that new medicines and a vaccine to prevent or treat Toxoplasmic eye diseases. El Bissati received numerous awards including the NIH PRIDE Award (2012-2014) and granted 2 patents.

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