THE ROLE OF COENZYME-Q_{10} IN THE REGULATION OF INFLAMMATORY IMMUNE RESPONSES DURING EXPERIMENTAL CEREBRAL MALARIA IN MICE

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DECLARATION

This thesis is my original work and has not been presented in any other institution for a degree award or other qualification.

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How oblivious I was to the fact that reaching the finishing line needed strenuous effort, passion and hard work. However, owing to the vision of my beloved mother who always supported me through thick and thin, my thesis is finally complete. I would like to dedicate this thesis to my mother Florence Orwenyo without her dedicated support, this research and the entire PhD program in totality would not have been possible. I also dedicate this thesis to my siblings George, Christine, Nyabuto, Judy, Ali, Maureen and Esther who at all times provided unwavering courage and mentorship.

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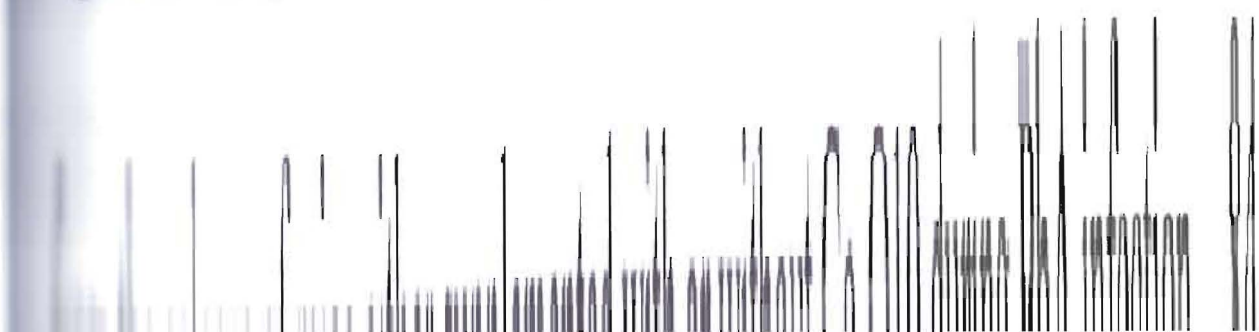

LIST OF ABBREVIATIONS

18s rRNA	18S ribosomal ribonucleic acid
8-OHDG	8-hydroxy-2deoxyguanosine
AAMs	Alternatively activated macrophages
ACT	Ammonium-chloride-Tris-buffer
ACT	Artemisinin combination therapy
ADCC	Antibody dependent cellular cytotoxicity
ALP	Alkaline phosphatase
Ang	Angiopoietin
BBB	Blood brain barrier
CM	Cerebral malaria (CM)
Co-Q_{10}	Coenzyme-Q_{10}
CO	Carbon monoxide
Ct	Threshold cycle
CTL	Cytotoxic T-lymphocytes
DAB	3.3, diaminobenzidine
DCs	Dendritic cells
DFO	Desferroxamine
ECM	Experimental cerebral malaria
ECP	Eosinophil cationic protein
EDN/EPX	Eosinophil derived neurotoxin/eosinophil protein X
ELISA	Enzyme linked immunosorbet assay
EPO	Eosinophil peroxidase
FACS	Fluorescence activated cell sorting
gMFI	Geometric mean fluorescent intensity

IKK	IκB kinase
IL	Interleukin
ILC	Innate lymphoid cells
INF-γ	Interferon gamma
IP-10	IFN-γ-inducible protein 10
IRBC	Infected red blood cells
IκBα)	Inhibitor kappa B
LFA-1α	Lymphocyte function-associated antigen-1
LTC4	Leukotriene C4
LTi	Lymphoid tissue-inducer cells
MACS	Magnetic activated cell sorting
MAPK	Mitogen-activated protein kinase
MBP	Proteins major basic protein
MCP-1	Monocyte chemotactic protein
MDA	Malondialdehyde
mDCs	Myeloid dendritic cells
MIG	Monokine induced by IFN-γ
MMP-9	Matrix metalloproteinases-9
MPTP	1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine
mtDNA	Mitochondrial DNA
NAC	N-Acetylcystein
NADPH	Nicotinamide adenine dinucleotide phosphate reduced
NCR	Natural cytotoxicity receptor
NF-κB	Nuclear factor kappa B
NK	Natural killer cells

PfEMP-1	*Plasmodium falciparum* erythrocytes membrane protein-1
PTRE	Post treatment reactive encephalopathy
Rag1	Recombination activating gene 1
RANTES	Regulated upon activation normal T cell expressed and secreted
RMCBS	Rapid murine coma and behavior scale
RORgt	RAR-related orphan receptors gamma
ROS	Reactive oxygen species
RPMI	Roswell Park Memorial Institute
sGOT	Serum glutamic oxaloacetate transaminase
sGPT	Serum glutamic pyruric transaminase
SOD-1	Superoxide dismutase-1
TBARS	Thiobarbituric acid reactive species
TGF-β	Transforming growth factor beta
T_H	T helper
TLR	Toll like receptor
TNF-α	Tumor necrosis alpha
TSLP	Thymic stromal lymphopoietin
UCPs	Uncoupling of proteins

LIST OF APPENDICES

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ABSTRACT

Cerebral Malaria (CM) is a form of malaria that causes a complex neurological syndrome, whose pathology is mediated by severe inflammatory processes triggered by the immune system of the host following infection with *Plasmodium falciparum*. There is limited progress in the development of new approaches for the treatment of CM. The aim of this study was to systematically elucidate the putative impact of oral administration of Coenzyme-Q_{10} (Co-Q_{10}) on the initiation or regulation of inflammatory immune response in experimental cerebral malaria (ECM). In addition, the ability of Co-Q_{10} to assuage ECM-induced inflammation and oxidative stress was determined. For this purpose, one group of C57BL/6J mice was used as control; the second group was infected with *Plasmodium berghei ANKA* (PbA) and the third group of mice were orally supplemented with 200mg/kg Co-Q_{10} and then infected with PbA. Within this experimental set up, a series of experiments were carried out in concert with the study objectives. They included: survival analysis, extensive clinical and biochemical analyses, flow cytometry, real time PCR for mRNA levels, immunoblot and immune-based assays. It was observed that oral administration of Co-Q_{10} both before and after PbA infection protected majority of mice against ECM. Importantly, Co-Q_{10} supplementation significantly hampered infiltration of inflammatory monocytes, T cells and cytotoxic granzyme B into the brain. Brain tissue analysis showed a reduction in the expression levels of inflammatory transcripts TNF-α and MIP-1β in Co-Q_{10} administered mice. Furthermore, Co-Q_{10} administration resulted in decreased expression of chemokines (CXCL9, CXCL10) in the brain, leading to reduced levels of activated pathogenic T cells with concomitant improvement in blood brain barrier disruption. In addition, Co-Q_{10} modulated the differentiation and maturation of both splenic and brain dendritic cells during ECM. Notably, anti-inflammatory cytokines IL-10 and IL-22 together with T-regulatory cells, which are associated with protection during ECM, were up-regulated in Co-Q_{10} treated mice. Remarkably, Co-Q_{10} was very effective in decreasing NF-κB phosphorylation, which is associated with ECM pathology. Splenic analysis of innate lymphoid class two (ILC2), which are known to play a protective role during ECM, showed augmentation in the spleens of Co-Q_{10} administered mice. Meanwhile, levels of matrix metalloproteinases-9 and angiopoietin-1&2, which are linked to severity of CM were reduced in mice administered with Co-Q_{10}. Furthermore, Co-Q_{10} supplementation abrogated malondialdehyde, diene and 8-hydroxy-2deoxyguanosine (8-OHDG) which are markers of oxidative stress and DNA damage. Moreover,