The role of *Plasmodium falciparum* kinase eIK1 in the melatonin signal transduction pathways in the control of cell cycle

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Malaria is caused by the Apicomplexan parasite *Plasmodium falciparum*. It is asexual replicative cycle inside red blood cell is responsible for pathogenesis and induces several structural and biochemical changes within the host cell. Unraveling the mechanisms of signal transduction pathways engendered by the parasite is a fundamental question, considering the resistance to artemisinin and the urgency for development of new strategies to combat the disease. In eukaryotes the control of gene expression via protein phosphorylation kinases can interfere with gene transcription and translation. The eIF2\(\alpha\) factor is able to activate translation of mRNAs in response to unfavorable situations. In silico analyzes showed that *Plasmodium falciparum* genome encodes three protein kinases able to phosphorylate the eIF2\(\alpha\) and thus, modulate eIF2\(\alpha\) activity: PfeIK1, and PfeIK2 PfPK4. We have investigated the role of PfeIK1 in the melatonin signal transduction pathway using transgenic *P. falciparum* parasites (unable to express PfeIK1) by flow cytometry and the nucleic acid dye Yoyo-1. We found that PfeIK1\(^-\) is unable to respond to melatonin. These results lead us to investigate the role of kinases in melatonin signaling.

Using specify antibody to phospho-eIF2\(\alpha\) and western blot assays, we have found a significant increase in the phosphorylation levels of eIF2\(\alpha\) in PfeIK1\(^-\) parasites after 1 minute treatment with melatonin (100 nM) when compared with non-treated knockout parasites. This data lead us to conclude that melatonin is promoting the phosphorylation of eIF2\(\alpha\) through another kinase, in addition to PfeIK1. A time-point phosphorylation (1, 15 and 20 minutes) triggered by melatonin was performed in wild type and PfeIK1\(^-\) parasites. The results show that at one minute, higher levels of eIF2\(\alpha\) were phosphorylated while a decrease in the basal phosphorylation eIF2\(\alpha\) was observed in wild type parasites. This data suggests that the dephosphorylation state of eIF2\(\alpha\) might be relevant to parasite synchronization.