The Identification of ATPase Activity Regulation in Tetrahymena thermophila: Understanding the Function of the Malarial ATP Synthase in Order to Develop New Antimalarials

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Understanding the physiology of the malaria parasite is critical to developing new drugs to fight malaria. This study used Tetrahymena thermophila as a model organism to investigate a potential function of the malarial ATP Synthase. Mitochondrial ATP synthase is a molecular motor that uses a proton gradient to synthesize ATP. Though it normally operates in the forward direction, it can catalyze the reverse reaction, ATP hydrolysis. This ATPase activity is useful to maintain the vital mitochondrial membrane potential under certain conditions. Regulation of ATPase activity in response to mitochondrial membrane potential has not been identified in T. thermophila. To test for the presence of such regulation, the mitochondrial membrane potential of T. thermophila was reduced using the respiration inhibitor rotenone, and the resulting change in ATPase activity was assessed. Enzyme complexes from mitochondria isolated from rotenone treated and untreated T. thermophila were displayed by blue native gel electrophoresis. In-gel ATPase assays showed increased ATPase activity in the dimeric ATP synthase complexes of rotenone treated mitochondria relative to those of untreated mitochondria. These results demonstrate that reduction of mitochondrial membrane potential allows the ATP synthase to catalyze ATP hydrolysis. This ATPase activity regulation is likely present in other alveolates such as the malaria parasite, suggesting that the ATPase activity of the malarial ATP synthase serves to maintain the essential mitochondrial membrane potential. Therefore, ATPase activity regulation could be targeted in the development of new antimalarial drugs. Bioinformatics work identified a putative malarial ATPase inhibitor protein that can be explored in targeting this ATPase activity.

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