Structural Characterization and Mechanistic Insights into Pathogenic Fungal Acetyl-CoA Synthetases

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Invasive fungal infections have led to over 1.5 million deaths globally each year primarily in people with compromised immune systems and have an attributed cost estimate of $6.7 billion (2018) in the US alone. Current treatment options are limited due to the challenging development of new classes of antifungal drugs, of which only three have been developed in the last 50 years. As with antimicrobial drugs, resistance to current antifungal treatments is also a major issue. New drug targets are needed to combat the growing health crisis. With this in mind, we established a collaboration to structurally and functionally characterize Acetyl-CoA Synthetases (ACSs) from major pathogenic fungal species including Cryptococcus, Aspergillus, Candida and Coccidioides. ACSs belong to the Acyl-CoA/NRPS/Luciferase (ANL) superfamily of enzymes that catalyze formation of acetyl CoA through a two-step adenylation and thioesterification reaction mechanism. With the aid of small molecular inhibitors, we used crystallography to structurally characterize each step of the two half-reactions. We systematically evaluated a series of alkyl adenosine esters as chemical probes to also characterize the selectivity of these enzymes toward acetate over larger carboxylic acid substrates. These results highlight a key tryptophan as a selectivity filter which limits the size of potential substrates, effectively acting as a steric 'wall' which causes longer alkyl chains to adopt less favorable high energy conformations. Structural enablement of fungal ACSs opens exploration of a new class of antifungal drug targets critical to the central carbon metabolic pathways in invasive fungal species.

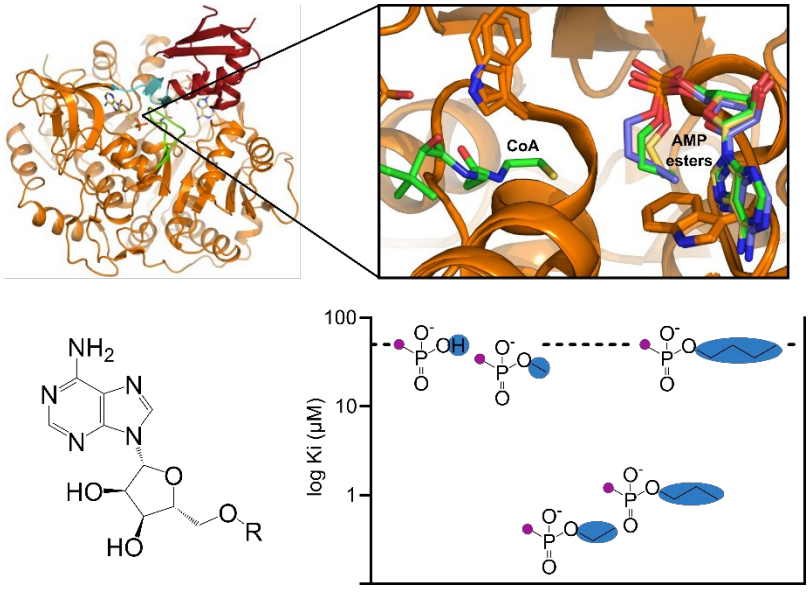

Figure 1