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# THE IMPORTANCE OF COENZYME A IN MITOCHONDRIAL FATTY ACID SYNTHESIS PATHWAY

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Mitochondrial biogenesis is a complex process, as it is composed of many pathways that communicate in coordination and are interdependent. The highly conserved mitochondrial pathway for fatty acid synthesis (mtFAS), has recently been shown to regulate late-stage assembly of the electron transport chain and how this pathway is regulated is the major question of this proposal (Nowinski *et al,* 2018.) The canonical fatty acid synthesis pathway (FAS I) occurs in the cytoplasm and generates fatty acids for membrane biosynthesis, hormones, and energy sources (Nowinski *et al,* 2018.) Interestingly, eukaryotes have maintained a second fatty acid synthesis pathway that occurs in mitochondria (mtFAS). Unlike FAS I, mtFAS does not contribute to the cellular fatty acid pool, but instead produces lipoic acid which is a cofactor for several dehydrogenase and more importantly, it has also been shown to be a major regulator for the assembly of the electron transport chain (ETC) (Nowinski *et al,* 2018.) Mitochondrial fatty acid synthesis involves many enzymes, substrates and cofactors, mitochondrial acetyl-CoA being the essential substrate for fatty acid synthesis. Acyl chains are synthesized by stepwise addition of carbon units. During the elongation process, the acyl carrier protein (ACP) acts as a main component upon which the growing chain is attached to the distal end of a 4'-phosphopantetheine moiety (4'PP) of ACP (Nowinski *et al*, 2018.) Therefore, the modification of ACP with its cofactor 4'PP is a crucial, early step that precedes acyl chain formation. Coenzyme A is utilized in order to attach 4'PP to the apo form of the acyl carrier protein, and the resulting complex (holo-ACP) is utilized as scaffold, where fatty acids attach as they elongate (Nowinski *et al,* 2018.)

Collaborators of the Rutter Lab performed a genome wide genetic screen called SATAY (saturated transposon analysis in yeast) under various nutrient-limiting conditions to identify genes that cluster with components of the mtFAS pathway. This unbiased screen identified that LEU5 clusters with the mtFAS genes. LEU5 is proposed to be a Coenzyme A transporter (Prohl *et al,* 2001.) This suggests that Coenzyme A (CoA) provided by LEU5 might play a role in regulating mtFAS. CoA is important in fatty acid synthesis, and therefore, plays an essential role in electron transport chain (ETC) biogenesis via the physical interaction of ETC complexes and the acyl-chain attached to 4'PP of ACP (Nowinski *et al,* 2018.) Data reports that when ACP is not bound to 4'PP, and as a result ACP is not acylated the mitochondrial fatty acid synthesis pathway is deactivated, and the ETC complexes are destabilized (Nowinski *et al,* 2018.) Hence, we hypothesize that mitochondrial CoA levels are at times limiting, which in turn regulates the mtFAS pathway by limiting the amounts of holo-ACP that is available to build acyl chains. The purpose of this research project is to investigate whether CoA levels are important in regulation of MtFAS pathway. Based on the data obtained from the collaborators of the Rutter Lab, we think that the CoA transporter LEU5 plays a crucial role in regulating mtFAS. In order to test the

hypothesis, we generated LEU5 KO strain. Future goals include spot testing to confirm the genotype, cloning *leu5* with endogenous promoter, testing whether *pLEU5* can rescue glycerol phenotype, cloning *leu5* into different plasmids contain different strength promoters and testing expression levels.

References:

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