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Sacromeric Mitochondrial Creatine Kinase, Muscle (sMtCK-MM)

Function

CK-MM is used to catalyze the reaction of creatine (Cr) + ATP → phosphocreatine (PCr) + ADP. This reaction is reversible and CK-MM and MtCK-MM work together to replenish ATP stores as shown in Figure 1 (Baird et al., 2012). ATP is hydrolyzed to release energy for muscle movement. As concentrations of ATP deplete and ADP increase in the cytosol, CK-MM catalyzes PCr to couple the synthesis of ATP and produces Cr as a byproduct. High concentrations of Cr in the cytosol diffuse into the mitochondria and ATP is catalyzed by MtCK-MM to produce more PCr. With assistance from the electron transport chain, ADP and Pi in the mitochondria undergo oxidative phosphorylation to replenish ATP stores in the muscle cells (Cooper, 2000). Bodybuilders and athletes commonly take creatine supplements to increase ATP regeneration to improve athletic performance and muscle growth.

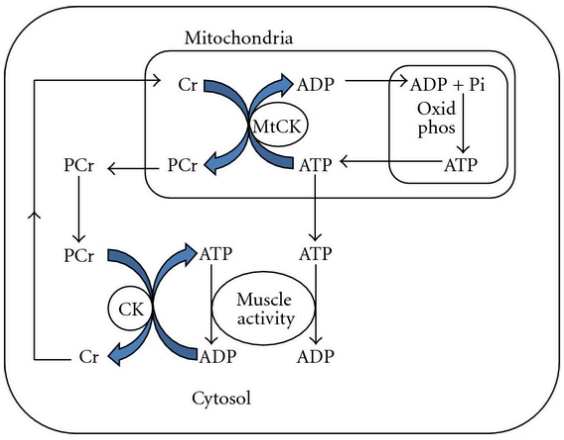

Figure 1 - Reversible reaction

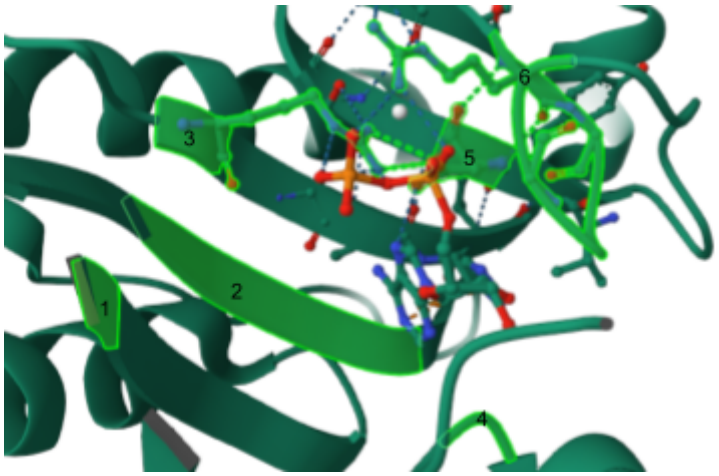

Figure 2 - CK-MM binding sites (not numbered in any order)

Structure

sMtCK-MM is composed of 392 amino acids (Rabeh et al., 2015). There are six binding sites found in positions 138/140/142, 201, 302, 306, 330/332, and 345. Four of these binding sites (138/140/142, 302/306, 330, 345) are part of a series of beta-pleated sheets found near the binding site as shown in Figure 2. The remaining sites (4, 6) are found in the peptide chains near the substrate. Arginine (140, 142, 302, 330), histidine (201), aspartic acid (345), serine (138), and threonine (332) are essential amino acids to the binding sites. The basic R-groups of arginine and histidine allow for ADP to bind through cation-pi and pi-stacking interactions respectively as depicted in Figures 3 and 4. Arginine's abundance of polar hydrogens allows for hydrogen bonds to form between ADP's slightly negative nitrogenous base. Aspartic acid has a carboxylic acid at the end of its R-group that plays a key role in stabilizing both ADP and Arg 302, a fellow binding site, as shown in Figure 5. Serine and threonine are neutral, and polar with hydroxyl groups that form additional hydrogen bonds with both the nitrogenous base and the ribose as shown in Figures 7 & 8. Ether linkages occur between the carboxyl in peptide linkages and the hydroxyl in the phosphate group as observed in Figure 8. CK-MM has the ability to bind to

multiple substrates in addition to ADP. However, research was only conducted for the six binding sites of ADP. No research about sMtCK-MM's active site was found. The prevalence of basic and polar binding sites correspond to the polar and negatively charged ADP molecule.

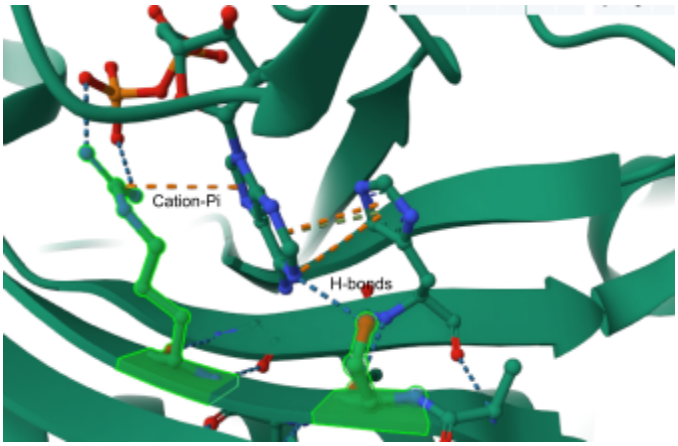

Figure 3 - Arginine 140 (left), Arginine 138 (right)

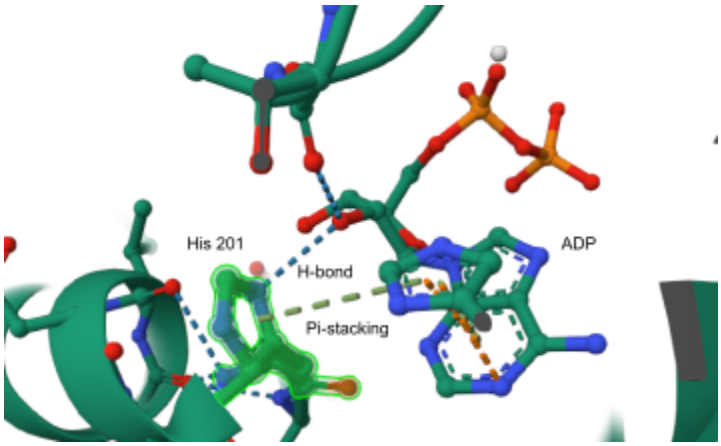

Figure 4 - Histidine 201

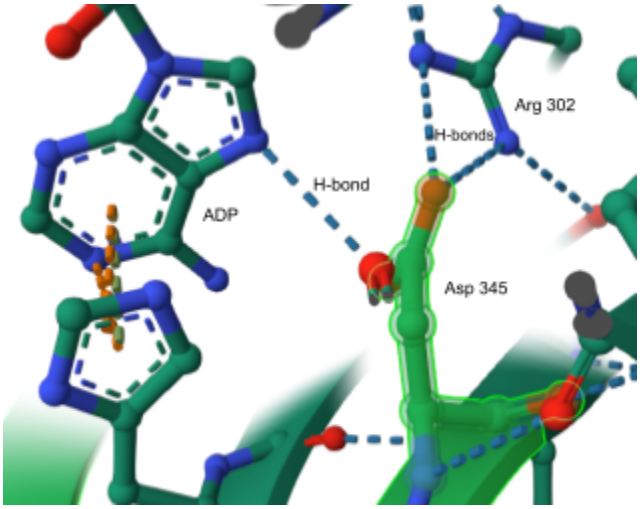

Figure 5 - Aspartic Acid 345

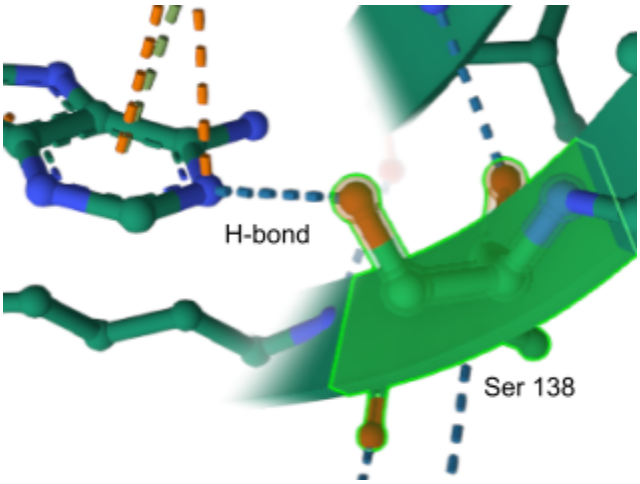

Figure 6 - Serine 138

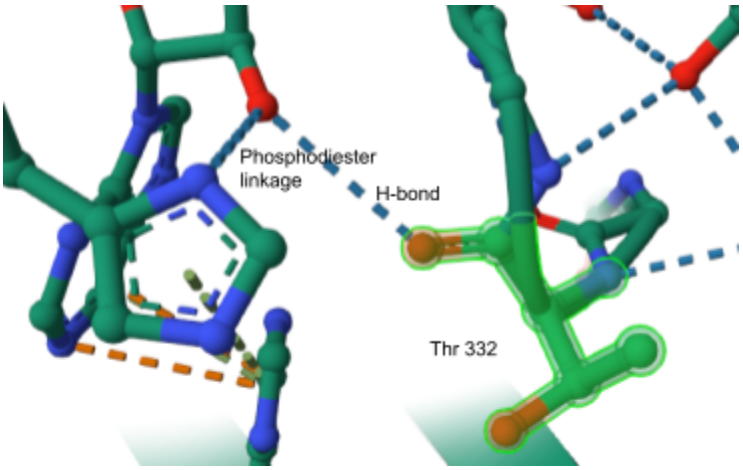

Figure 7 - Threonine 332

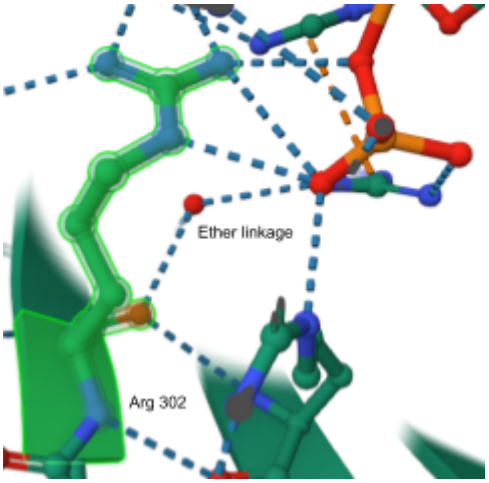

Figure 8 - Ether linkage

Stability

All isoenzymes of CK are known to increase enzymatic activity when skeletal muscle undergoes mechanical stress through aerobic exercise. A study conducted where CK activity was measured during 90-minute cycling exercise in three consecutive days revealed a significant increase in enzymatic activity, peaking on Day 2 (Ex. 2) as shown in Figure 9 (Totsuka et al., 2002). Contrarily, an experiment conducted showed that CK-MM in rabbit muscle denatured in lactic acid concentrations above 0.2mM and unfolded in concentrations of 0.8mM (Zhou et al., 2003). Lactic acid is produced by the body when the body lacks oxygen to phosphorylase ATP, suggesting that highly anaerobic activity is correlated to the instability of CK-MM. More specifically, the study suggests that acidic environments easily unfold CK-MM, but significantly low pH concentrations are needed to completely inactivate it.

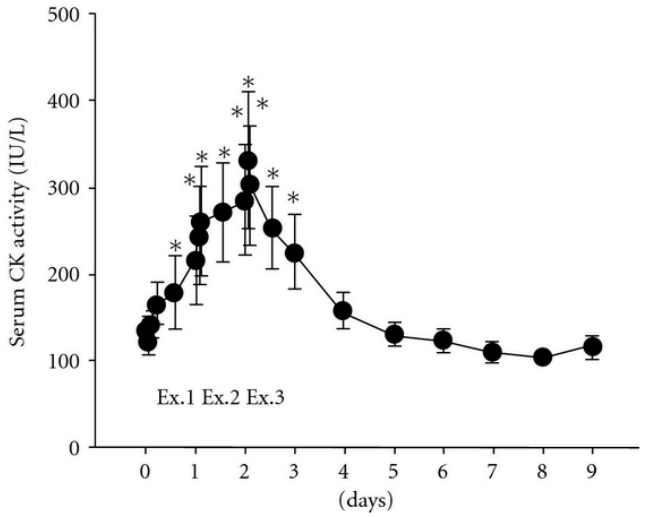

Figure 9 - CK activity during endurance exercise and rest

References

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