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Exploring the Catalytic Mechanism of the Malonyl-Acetyl Transferase Domain of Fatty Acid Synthase

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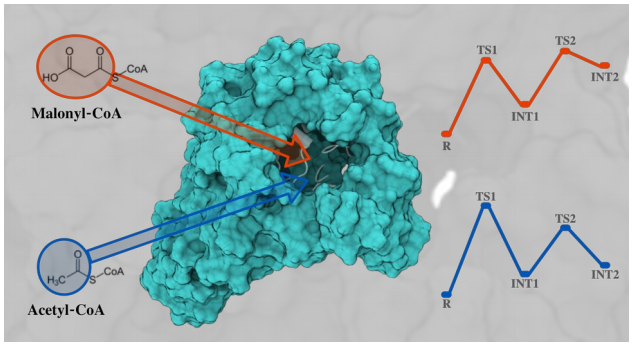
Graphical Abstract



Abstract.

Human fatty acid synthase (hFAS) is a multidomain enzyme that catalyzes all steps of fatty acid biosynthesis [1], which is deregulated in many varieties of human cancers. Studies have shown that FAS inhibitors exhibit anticancer activity without relevant side-effects over healthy cells [2]. Thus, the molecular characterization of all hFAS domains is an important goal for the development of novel anticancer therapies. The malonyl-acetyl transferase (MAT) domain loads acetyl and malonyl moieties to the phosphopantetheine arm of the acyl-carrier protein (ACP) domain, a carrier for reaction intermediates [3]. In this study, we have employed computational hybrid QM/MM methods at the DLPNO−CCSD(T)/CBS:AMBER level of theory [4] to study the MAT catalytic mechanism. The results indicate that the transfer of acyl moieties from CoA to MAT occurs in two catalytic steps: (1) concerted nucleophilic attack on the thioester carbonyl group of the substrate, centered on a Ser-His dyad and (2) tetrahedral intermediate breakdown. The Gibbs activation barrier of the first step is 13.0 kcal·mol−1 for the MAT-acetyl-CoA complex, and 10.9 kcal·mol−1 for the MAT-malonyl-CoA system. As for the second catalytic step, Gibbs energy barriers of 6.4 kcal·mol−1 and 8.0 kcal·mol−1 were obtained

	for the MAT-acetyl-CoA and MAT-malonyl-CoA complexes, respectively. Two hydrophobic residues, Phe553 and Phe682, are responsible for the positioning of the acetyl moiety in the active site. Additionally, persistent ionic interactions between Arg606 and the carboxylate anion of the malonyl moiety maintain the substrate in a catalysis-favorable position, which corroborates previous experimental findings [5]. The backbone amines of Met499 and Leu582 form an oxyanion hole that accommodates the negative charge of the substrate carbonyl, reducing the activation barrier of the first step for both substrates. The results from this work [6] instigate future studies that aim for the full understanding of MAT's catalytic machinery and that explore the therapeutic potential of hFAS.

Introduction *(optional)*

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Materials and Methods *(optional)*

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Results and Discussion *(optional)*

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Conclusions *(optional)*

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References *(mandatory)*

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[6] Paiva, P., Sousa, S.F., Ramos, M.J., and Fernandes, P.A., Understanding the Catalytic Machinery and the Reaction Pathway of the Malonyl-Acetyl Transferase Domain of Human Fatty Acid Synthase. ACS Catalysis 2018 8 (6), 4860-4872.