Computational modelling of the LCAT::rHDL complex and bases of LCAT pharmacological activation

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Abstract

LCAT is a liver-secreted protein that circulates in plasma reversibly bound to lipoproteins, where its main function is to catalyze cholesterol esterification, transferring an acyl chain from phosphatidylcholine to free cholesterol, thus playing a crucial role in HDL maturation and reverse cholesterol transfer.

Loss of function mutations in the LCAT gene may lead to LCAT deficiencies, rare monogenic disorders of lipid metabolism with important clinical consequences, for which no definite cure is available. Despite the effectiveness of recombinant enzyme replacement therapy, the viability of a small molecule-based approach to treat LCAT deficiencies would provide superior advantages to patients in terms of an improved quality of life and lower social costs.

Preliminary results show that small molecules (SM) with allosteric activating mechanism may operate LCAT mutants *in vitro*, thus, the aim of this project is to rationalize the *in-silico* design of LCAT activators that could partially restore enzyme activity in carriers of defective LCAT.

We took advantage of recently published crystallographic data of LCAT and apo-AI structures and assembled the LCAT::rHDL supramolecular complex with a chimeric model of a reconstituted HDL (rHDL); using molecular dynamics, stochastic sampling, protein::protein docking and other bioinformatics tools, we provided a data-driven general model of LCAT activation by apo-AI and a study of the dynamic behavior of LCAT subdomains critical to catalytic site accessibility and interaction with HDLs. Models were validated in light of recently published cryo-EM, HDX and XL-MS data, shedding light on the interactions between LCAT and rHDLs. We then used the generated architecture to provide a mechanistic explanation of the activity loss in LCAT mutants and to understand how novel activators can restore their functionality. We analyzed the binding mode and the affinity of two published LCAT activators, and rationalized their mechanism of action, laying the foundations for the rational drug design of SM activators.