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Drug targets and lipid biomarkers of hyperlipidemia associated diseases

Sneha Rai[1] and Sonika Bhatnagar[2*]

[1,2]Computational and Structural Biology Lab, Biological Sciences and Engineering, Netaji Subhas Institute of Technology, Dwarka Sector – 3, New Delhi 110078, INDIA

*Corresponding author: ecc999@gmail.com

Abstract

Hyperlipidemia (HL) is characterized by elevated level of plasma lipids affecting regular functioning of lipid-protein interactions leading to disease. The traditional lipid biomarkers utilized for detection of individuals with HL and Cardiovascular Diseases (CVD) risk, sometimes fail to predict future CVD events therefore, establishing need of novel lipid biomarkers for CVD detection. It was attempted to predict the lipid biomarkers using systems biology and by a meta-analysis of lipidomics studies. A lipid-protein-protein interaction network (LPPIN) was built by incorporating differentially expressed genes in fatty liver of obese subjects obtained from Gene Expression Omnibus, with the interacting lipids obtained from STITCH database. The protein interactions were derived using PathwayLinker and lipid interactions were acquired from STITCH 4.0. For identification of novel lipid biomarkers comparative analysis of normolipidemic, hyperlipidemic and CVD lipid profile was conducted. Cholesterol, diacylglycerol, phosphatidylinositol-bis-phosphate and inositol-triphosphate were central to LPPIN, therefore had the largest systemic effect. The choke point analysis identified proteins having maximum interactions with network lipids, malfunctioning of which could lead to HL associated diseases. Cluster analysis recognized CVD, cancer, Alzheimer's disease and type-2-diabetes to be linked with HL. Lipids associated with the disease clusters consisted of triacylglycerol, cholesterol, oleic acid, linoleic acid, arachidonic acid, palmitate, inositol triphosphate, inositol-1,4-bisphosphate and phosphatidinositol-4-phosphate. Approved HL drug targets like Proprotein Convertase Subtilisin Kexin Type 9 and Niemann-Pick C1-Like 1 may be repurposed for treatment of hyperlipidemia associated diseases. Using a combination of gene prioritization and bridging centrality, Coactosin-like binding protein 1, Vasodilator stimulated phosphoprotein and Hedgehog acyltransferase were identified as a potential drug target for CVD, cancer and Alzheimer's, respectively. A comparative lipidomics analysis revealed that palmitoyl-lysophosphatidylcholine level was decreased while plasma level of free fatty acids and ceramides were elevated in HL and CVD. Both HL and CVD were associated with changes in lipid composition. HL was associated with increased level of saturated diacylglycerol, triacylglycerol and phospholipids while CVD was associated with increase in small chain fatty acids with low double bond content in triacylglycerol, cholesteryl ester and sphingomyelin. Our work highlights new drug targets and biomarkers for hyperlipidemia.

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