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Integrated Lipid-Protein Interaction Network for Study of Hyperlipidemia: Pathogenesis, Progression and Drug Targets

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Abstract—*The incidence of acquired hyperlipidemia (AH) has increased in recent times due to sedentary life style and unhealthy diet. AH may become an underlying cause for multiple diseases due to aberrant lipid signaling. In this work, a lipid-protein-protein interaction network (LPPIN) was constructed by integrating differentially expressed genes in fatty liver of obese subjects with the interacting lipids in order to obtain an integrated network view of the underlying processes. The differentially expressed genes were mined from Gene Expression Omnibus, protein interactions were obtained using PathwayLinker and lipid interactions were mined using STITCH 4.0. The interactions were combined using Cytoscape 3.2.0 and KOBAS 2.0 was used for further annotation of the network proteins. The LPPIN showed that a large number of dietary lipids interacted at the periphery of the network in various metabolic processes while only a few signaling lipids interacted with the core. Cholesterol, inositol-triphosphate, phosphatidylinositol-bis-phosphate, and diacylglycerol were highly interacting central signaling lipids involved in pathogenesis of AH. Choke point analysis revealed proteins critical for lipid signaling. Mutations in these proteins are likely to lead to AH associated pathologies. Pathway analysis identified the novel role of Gastric-Creb signaling pathway in pathogenesis of hyperlipidemia. All the signaling pathways were involved in crosstalk with PI3K-Akt signaling pathway. Disease nodes for CVD, Alzheimer's, Cancer and Type-2-Diabetes were over-represented in the LPPIN and approved hyperlipidemia drug targets that may be repurposed for treatment of these diseases were proposed. A combination of network topology features and candidate gene prioritization approach was employed to locate novel potential drug targets for therapeutic treatment of AH associated diseases. The main pathways in each disease cluster were identified and can be targeted for treatment. The common and unique interacting lipids associated with the disease clusters represent molecular diagnostic signatures for AH and its associated disorders.*