Ph.D. Pre-synopsis Seminar

Title: Identification of enriched biochemical networks and polypharmacological targets for metabolic syndrome

Name: Ms. Indra Kundu
Division: Biomedical Informatics Centre
Research Guide: Dr Susan Thomas
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Venue: Shanta Rao Auditorium

Abstract

Metabolic syndrome (MetS) is a complex disorder characterized by cluster of metabolic abnormalities including obesity, hyperglycemia, dyslipidemia and hypertension. According to harmonised definition of MetS, individuals having 3 out of 5 components (obesity, hyperglycaemia, hypertension, high triglycerides and low HDL) are diagnosed with MetS. The prevalence of MetS in Indian adult population is ~30% and it steadily increases with increase in age. Individuals with MetS have multiple comorbidities including diabetes, PCOS, NAFLD and have elevated risk of developing cardiovascular diseases. Current therapeutic strategies largely focus on managing individual components using antihypertensive drugs, statins, anti-obesity medications, biguanides, and antiplatelet agents. However, given the complex and interconnected nature of MetS, studying the syndrome as an integrated metabolic entity may provide deeper insights into its pathophysiology.

To address this, we developed a comprehensive knowledgebase (MetSKB) integrating information on genes, non-coding RNAs, epigenetic modifications, biochemical, and anthropometric parameters associated with MetS. Meta-analysis of gene expression datasets and genome-wide association studies (GWAS) identified key genes and pathways including ferroptosis. Furthermore, a computational framework (GeDiPNet) was constructed to predict polypharmacological targets; this framework underwent initial validation utilizing established drug targets before being employed to forecast both existing and prospective therapeutic candidates for MetS.

Subsequently, selected genes from MetSKB, meta-analysis findings, and predicted polypharmacological targets were further examined through a genome-scale metabolic model to ascertain their systems-level metabolic effects. The in-silico knockout study demonstrated coordinated shifts in amino acid metabolism, mitochondrial substrate utilization, and lipid handling. These predictions were corroborated by metabolomics data

from clinical samples, which confirmed metabolites such as hydroxyproline, saccharopine, aminoadipate, and acyl-carnitines as potential metabolic signatures of MetS.

Overall, this study employed multi-omics data mining and analysis, computational target prediction, and metabolic modeling to identify crucial molecular regulators and metabolic pathways implicated in MetS. Future efforts will be directed to validate the predicted biomarkers and targets within independent clinical cohorts to facilitate the development of therapeutic strategies for the management of MetS.