A MULTIOMIC APPROACH FOR THE ANALYSIS OF TRIBUTYLTIN-EXPOSED ADIPOCYTES REVEALS OMIC-RELATED SIGNATURES ASSOCIATED WITH METABOLIC DISORDERS

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ABSTRACT

Metabolic syndrome is a cluster of frequently co-occurring conditions linked to various health outcomes and is increasingly attributed to exposure to endocrine-disrupting chemicals (EDCs). Interestingly, EDCs may impact the normal development and function of adipose tissue, which was once considered an inert storage depot, although mounting evidence suggests that it is a complex and metabolically active organ with a considerable influence on the regulation of metabolism and energy homeostasis. To explore relevant effects of EDCs on metabolic outcomes, Simpson-Golabi-Behmel syndrome (SGBS) pre-adipocytes were exposed to tributyltin (TBT), a known lipogenic substance, to map the omic-level signature associated with metabolite and transcript dysregulation. SGBS pre-adipocytes were grown to near confluence and incubated in differentiation medium for four days, followed by cultivation in maintenance medium for six days. The differentiation medium of TBT-exposed cells was additionally supplemented with 25nM TBT during the initial four days. Cells were harvested on day 10 of differentiation and TBT-exposed and differentiated controls were compared. Transcriptomic analysis was performed using Agilent microarrays to determine differentially expressed genes (DEGs) between treatment groups. Samples for untargeted metabolomics were analyzed using Reversed Phase (RP) and Hydrophilic Interaction (HILIC) Liquid Chromatography in positive and negative ionization modes. Data preprocessing, batch correction, and statistical analyses were conducted in R using xcms, IPO, PMCMRplus, and xMSannotator packages for metabolomics, and limma for transcriptomics. An integrated omics analysis pipeline was employed, using univariate and multivariate approaches in mixOmics and MetaboAnalystR, aimed at enhancing the depth of understanding of multiomic mechanisms. This approach highlights both individual molecular changes and their integrated effects on cellular pathways. Across analyses, perturbations in pathways linked to metabolic dysfunction, including dyslipidemia, obesity, and inflammation, were consistently identified. The identification of key features and shared perturbed pathways provides a foundation for further mechanistic investigations and

potentially informs strategies for mitigating the adverse effects of these exposures. Future studies will delve deeper into the adipocyte 'ome', seeking indications of susceptibility or early warning signs specific to health outcomes such as metabolic syndrome.

KEYWORDS: transcriptomics, untargeted metabolomics, multi-omics, endocrine disrupting compounds, environmental health