Lipid exposure re-wires cellular metabolism away from glycolysis toward the serine pathway conferring oncogenic properties to non-transformed breast cells

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Introduction

• Understanding the genesis of sporadic estrogen receptor-negative breast cancer (ERnegBC) is a significantly unmet clinical need.
• Genes involved in lipid metabolism are overexpressed in the contralateral unaffected breast of women with ERnegBC (1).
• Exposure of non-transformed breast epithelial cells to lipids results in significant changes in histone PTMs and gene expression. The upregulated genes are involved in neural pathways and stemness (2).
• In vitro, lipid exposure alters histone methylation affecting gene expression and increases flux through various metabolic reactions including those involved in serine, one-carbon, glycine (SOG) and methionine (2).
• We hypothesized that the metabolism of lipids in preference to glucose and glutamine results in a metabolic shift in the serine pathway increasing S-adenosylmethionine (SAM) leading to histone methylation increases and changes in gene expression.

Methods

• 13C-glucose tracing was performed in MCF-10A cells exposed to octanoic acid (OA). Targeted metabolomics was performed in MCF-10A cells exposed to OA ± PHGDH inhibitor or siRNA against PHGDH.
• ROS-induced redox changes were monitored using ORP1-roGFP2 based sensors in MCF-10A cells
• Alkaline comet assay was done to detect DNA breaks.
• Homologous recombination was studied in MCF-10A cells through restoration of homologous recombination in numerous cell clusters
• Cut&Run for H3K4me3 was performed in MCF-10A exposed to OA. MACS2, DiffBind and ChIPseeker were used to call and annotate peaks. HOMER was used for Transcription factor (TF) binding motif enrichment analysis.
• Single-cell RNA-seq (scRNA-seq) was performed on primary human breast epithelial cells exposed to OA. The digital expression matrix file containing UMIs was analyzed with the Seurat package. Cell-cell communication was explored using CellChat and metabolic flux analysis was performed using Compass.

Results

Metabolism of lipids in preference to glucose and glutamine results in a metabolic shift toward the de novo serine pathway increasing the production of 2-HG (A), glutathione (B) and SAM (C) which have implications for oncogenesis

References


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