Sphingosine Kinase 2 Modulates DNA Damage and Immune Pathways in Triple-Negative Breast Cancer Cells

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Introduction. Triple-negative breast cancer (TNBC) is aggressive and lacks targeted therapies. Damaged DNA from radiation or chemotherapy can elicit anti-tumor immune responses. The immunomodulatory biolipid sphingosine-1-phosphate (S1P) is produced by sphingosine kinase 2 (SPHK2), which is elevated in TNBC. Global protein pathways regulated by SPHK2 in TNBC, especially regarding DNA damage immune responses, are unknown. In this study, we globally analyzed protein pathways that SPHK2 modulates using a mouse TNBC model.

Methods. We engineered the mouse TNBC cell line KPB25L to stably overexpress lentiviral vectors with SPHK2 (SPHK2-OE) or scrambled control, and we performed mass spectrometry proteomics. Cellular pathways were analyzed and visualized using Metascape and Cytoscape.

Results. Proteomic analysis detected 4,726 proteins total. 435 proteins were significantly increased and 303 were significantly decreased in SPHK2-OE compared to control cells. SPHK2 expression was increased by a fold-change of 4.623 in SPHK2-OE. The proteins increased in SPHK2-OE were significantly enriched for pathways including protein localization, chromatin remodeling, positive cell cycle regulation, and autophagy. DNA damage enriched pathways include DNA damage/telomerase stress induced senescence, negative regulation of DNA recombination, and regulation of cellular stress responses. Additionally, enriched immune pathways include tumor necrosis factor receptor signaling and regulation of interferon beta production.

Conclusions. Elevated SPHK2 in intrinsic tumor cells perturbed several pathways involved in the DNA damage and immune responses. This study warrants further understanding of SPHK2 modulation for therapeutic potential in TNBC.