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# Elucidation of novel therapeutic targets in melanoma influencing mitochondrial biogenesis via STAT6

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An altered mitochondrial function is a hallmark of cancer including melanoma. A mild mitochondrial dysfunction may enhance the growth and invasion of cancer cells while a severe dysfunction may cause cell death to inhibit tumorigenesis. Although several genes, including MCL1, SIRT3, BRAF, SOX2, TRAP1, and PTEN, are recognized as factors have respective mitochondrial roles in melanoma plasticity, other key factors have not been clearly identified, and the intricate mechanisms governing mitochondrial responses remain poorly understood.

In previous study, we found that STAT6 down regulation increased mitochondrial mass in B16F10 melanoma cell lines, indicating that STAT6 regulates mitochondrial biogenesis in melanoma. Given these observations, to pinpoint potential therapeutic markers influenced by central regulators of mitochondrial responses and energetics, we sought to identify mitochondrial gene markers that impact patient survival via the modulation of STAT6. We stratified the samples into two primary groups (STAT6-H/L) based on the median expression value of STAT6, derived from RNA-seq data encompassing 40,727 genes and clinical information from 470 melanoma patients sourced from TCGA. We identified 322 and 417 DEGs in the STAT6-H and STAT6-L groups, respectively, by comparing with melanoma RNA-seq data and three normal samples. Of these, 23 and 26 mitochondrial genes, respectively, intersected with a list of 1,837 mitochondrial genes curated from Amigo and a meta-analysis. We conducted survival analysis using the hazard function, specifically aiming to identify genes that modulate patient survival through the regulation of mitochondrial

function via STAT6 expression. In our analyses, the genes BLOC1S1, HIF1A, ACADS, SUCLG2, CRAT, NDUFB6, NUDT5, and BCL2 were significantly associated with survival in the STAT6-L group. Especially, NDUFB6 is required for Complex I activity in mitochondrial respiratory chain. Complex I deficiency is one of the most frequent dysfunctions of the mitochondrial respiratory chain in human. BCL2 is a target gene for Navitoclax, which is undergoing clinical trials for its efficacy of melanoma. The novel target genes identified in our analysis are anticipated to elucidate STAT6-mediated mitochondrial biogenesis and offer therapeutic perspectives for melanoma.