(PB3956) ATP5E LACTYLATION MEDIATED BY TP53 MUTATION PROMOTES PROGRESSION OF DIFFUSE LARGE B-CELL LYMPHOMA

Topic: 21. Lymphoma biology & translational research

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Background

TP53-mutant diffuse large B-cell lymphoma (DLBCL) is associated with poor prognosis and inferior therapeutic response. Lactylation (Kla) is a newly identified post-translational modification, playing critical roles in tumor progression. However, the extent and regulatory mechanisms of aberrant Kla in TP53-mutant DLBCL remain unclear.

Aims

This study aims to elucidate how mutant TP53 (MUT-TP53) affects lactate production and lactylation in DLBCL and to pinpoint key lactylation targets connecting MUT-TP53 to mitochondrial changes and cancer progression.

Methods

TP53 mutation spectrum in DLBCL was sourced from IARC TP53 database. RNA-seq identified transcriptional changes linked to TP53 alterations. Serum lactate levels were compared between DLBCL patients and healthy controls, with tissue Kla levels analyzed for correlations with progression-free survival (PFS) and overall survival (OS). Quantitative proteomics identified lactylated substrates, highlighting ATP5E Lys44 lactylation (K44la) as a potential modification. Statistical significance was determined using two-sided tests with $P<0.05$.

Results

In DLBCL, TP53 mutations mainly occur in Exon 5, leading to varied TP53 protein expression compared to naive B-cells. TCGA data reveals high activity in oxidative phosphorylation pathways in TP53-mutated DLBCL patients. RNA-seq shows enhanced metabolism, cell cycle, and DNA replication in DLBCL. Knocking down mutant TP53 doesn't affect the cell cycle but reduces LDHA expression, lactate levels, and APR-246 sensitivity. Conversely, knocking down wild-type TP53 boosts cell proliferation and shortens the G0/G1 phase. APR-246 treatment decreases lactate production and induces cell cycle arrest.
We observed higher serum lactate levels and increased Kla in DLBCL tissues, correlating with poorer survival. DLBCL cell lines exhibited significant Kla. Sodium lactate enhanced Kla, whereas glycolysis or LDH inhibition reduced it. Proteomics identified lactylated proteins involved in cell cycle, mitochondrial function, transcription, and signaling, with ATP5E's K44 being a key Kla site. We investigated the role of ATP5E K44la in DLBCL, finding that ATP5E is overexpressed and further increased by LNa treatment, with K44la boosting its expression. Overexpressing WT ATP5E promoted cell growth, while the K44R mutation suppressed it. DEGs related to ATP5E WT and K44R were linked to DNA replication, mitochondrial function, cell cycle, and OXPHOS. WT cells had lower mtDNA, higher mitochondrial membrane potential, reduced mtROS, and increased ATP, whereas K44R reversed these. Mass spectrometry showed TP53 interacts with ATP5E. MUT-TP53 knockdown, but not WT-TP53, reduced Kla. mIHC confirmed TP53 and Kla co-localization in DLBCL. ATP5E overexpression strengthened its interaction with TP53, while K44 mutation weakened it. Functional tests revealed MUT-TP53 knockdown increased mtROS and decreased mitochondrial membrane potential, suggesting TP53 mutation raises Kla in DLBCL.

Summary/Conclusion

MUT-TP53 creates a lactate-lactylation pathway in DLBCL by increasing LDHA/lactate and promoting ATP5E K44la, which stabilizes ATP5E, boosts mitochondrial remodeling, and supports tumor growth. This highlights lactate metabolism, lactylation, ATP5E K44la, and mutant-p53 as potential therapeutic targets.