AI-Optimized Machine Learning and Multi-omics Integration Identify ACADL as a Therapeutic Target in Pancreatic Cancer

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Abstract

Objective: Pancreatic cancer (PAAD) is characterized by poor prognosis and limited effective therapeutic options. Mitochondrial dysfunction plays a critical role in its progression. This study aimed to identify and validate the mitochondrial-related key gene ACADL using an artificial intelligence (AI)-driven integrative framework and to explore potential small-molecule inhibitors targeting ACADL. *Methods:* Transcriptomic data from TCGA, GTEx, and GEO databases were integrated to identify differentially expressed genes (DEGs) between tumor and normal tissues. Mitochondria-related genes were further screened through intersection analysis. Weighted gene co-expression network analysis (WGCNA) was applied to identify modules associated with tumor traits. Machine learning models, including LASSO and support vector machine (SVM), were constructed with cross-validation and hyperparameter tuning to identify robust hub genes. Cox regression and SHAP analysis were performed to evaluate the prognostic value and model contribution of ACADL. At the single-cell level, a large-scale pancreatic cancer single-cell atlas (~700,000 cells) was analyzed using the Seurat pipeline (SCT normalization, Harmony batch correction, UMAP dimensionality reduction, and clustering) to determine the cellular distribution of ACADL. Subsequently, approximately 500,000 compounds were subjected to virtual screening and molecular docking targeting ACADL. Molecular dynamics (MD) simulations were performed to assess the stability and interaction patterns of the protein–ligand complexes. *Results:* ACADL was significantly upregulated in pancreatic cancer tissues and was associated with advanced tumor stage and poor prognosis. WGCNA revealed that ACADL-associated modules were highly correlated with tumor progression and enriched in oxidative phosphorylation, energy metabolism, and hypoxia-related pathways. Machine learning models identified ACADL as a key predictive feature with strong diagnostic and prognostic performance (AUC > 0.85), which was further supported by SHAP analysis. Single-cell analysis demonstrated that ACADL was predominantly expressed in ductal/epithelial cells and showed elevated expression in specific stromal subpopulations. Virtual screening and molecular docking identified several candidate compounds, among which D001-lig_12580 exhibited strong binding affinity. MD simulations confirmed that D001-lig_12580 formed a stable complex with ACADL, characterized by favorable conformational stability and key hydrogen bond interactions. *Conclusion:* This AI-driven multi-omics and single-cell integrative study identifies ACADL as a critical regulator in pancreatic cancer and highlights D001-lig_12580 as a potential targeted inhibitor. These findings provide new insights into the molecular mechanisms of pancreatic cancer and offer promising directions for precision therapeutic development.

Keywords

Pancreatic Cancer, ACADL, Mitochondrial Dysfunction, Single-cell RNA Sequencing, Machine Learning, Multi-omics Integration, Molecular Docking, Molecular Dynamics