Decoding PDAC: A scRNA-seq Omics Analysis to Unveil and Inhibit Key Protein Using a Novel in-silico, Structure-Based Drug Design Pipeline

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Pancreatic Ductal Adenocarcinoma (PDAC), responsible for over 90% of pancreatic cancer cases, remains one of the most lethal cancers due to stage IV diagnosis and five-year survival rate of 13%. The only approved blood-test biomarker, CA 19-9, is used to monitor disease progression, but lacks early diagnostic utility. Compounding the problem, Gemcitabine chemotherapy has response rates between 6–11%, underscoring the need for novel early diagnostic biomarkers and therapeutics. To address this, single-cell RNA-seq analysis of PDAC and adjacent healthy tissue samples was conducted, revealing S100A6 as significantly upregulated in both ductal- and acinar-origin PDAC tumors. S100A6 is expressed after stage I in the blood and drives the epithelial-mesenchymal transition (EMT), activating beta-catenin, and upregulating N-cadherin, enhancing tumor metastasis. S100A6 was therefore selected as a novel biomarker and therapeutic target. Using a structure-based in-silico drug design approach, twenty novel small molecules designed to target S100A6 were generated in the LEA3D web server, ranked using a custom scoring function, and the top two candidates were further analyzed. The lead compound exhibited strong binding affinity (-6.311 kcal/mol) and favorable interactions with S100A6. Normal Mode Analysis confirmed protein-drug stability and favorable drug-induced conformational changes. ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) testing identified optimal pharmacokinetic profiles in lipophilicity, solubility, bioavailability, and drug-likeness, and minimal predicted toxicity. Therefore, S100A6 shows promise as a novel early diagnostic and therapy target for PDAC with a proposed therapeutic to be further evaluated with lead optimization and in vitro assays.

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