The Repurposing of Prednisolone: Inhibition on the Formation of Pancreatic Cancer Associated Fibroblasts (CAFs) Through Ets1-HMGXB3 Axis

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Pancreatic cancer is one of the deadliest diseases in the world. Cancer-associated fibroblasts (CAFs) are an important component of the tumor microenvironment (TME) and important immune-negative regulatory cells, playing a key role in tumor cell proliferation and metastasis. However, previous pancreatic cancer therapies such as surgery, radiation therapy, or chemotherapy are expensive and have severe side effects. The aim of this study was to screen for risk genes in pancreatic CAFs, find upstream targets, screen for drugs, and ameliorate the structure to target pancreatic CAFs. Based on Normal fibroblasts and serum-induced CAFs cell model, this study starts with performing RNA sequencing, proteomics and RT-qPCR analyses, which identified HMGXB3 as the crucial genetic signature in pancreatic CAFs. Further bioinformatic analysis unveiled Ets1 as a prime candidate transcription factor for HMGXB3. Targeting the upstream transcription factor Ets1, the drugs were screened by automated docking software, molecular dynamics software, and CCK8 experiments. It was found that prednisolone, a drug targeting CAFs, had a significant inhibitory effect on CAFs, whereas it did not have a significant inhibitory effect on normal fibroblasts. The targeting effect of prednisolone on Ets1-HMGXB3 axis was further verified by Western blot and RT-qPCR analysis. Study on the concentration gradient of prednisolone revealed 60μM as the most effective concentration. Finally, Molecular Operating Environment (MOE) software simulated possible structural improvements of the drugs. Overall, this study illuminates that prednisolone is an effective potential candidate for the treatment of pancreatic cancer by targeting the Ets1-HMGXB3 axis of pancreatic CAFs.

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