Physico-Chemical Characterization of the Tumour Microenvironment of Pancreatic Ductal Adenocarcinoma

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Summary

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive lethal malignancy that accounts for more than 90% of pancreatic cancer diagnoses. Our research is focused on the physico-chemical properties of the tumour microenvironment (TME), including its tumoural extracellular matrix (tECM) and its impact on the development of new therapies.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most prevalent form among all pancreatic cancer types. PDAC develops in the exocrine compartment of the pancreas and presents a high mortality rate due to late diagnosis as well as a limited response to conventional treatments, which include chemotherapy, surgery and radiotherapy [1]. Although immunotherapies are providing promising and optimistic results in several solid tumours, PDAC displays a non-immunogenic, immune-suppresive and therapy-resistant microenvironment [2] [3]. This is largely attributed to the intricate tumor microenvironment (TME) of PDAC, which plays a critical role in tumor progression and therapeutic response according to recent studies [4] [5]. Our study aims to characterize the physico-chemical properties of the PDAC tumor microenvironment using patient-derived xenografts and advanced decellularization techniques. By understanding these properties, novel therapeutic strategies may be developed to target PDAC more effectively and improve patient outcome.

Materials and methods

Patient-derived pancreatic ductal adenocarcinoma xenografts (PDX) were decellularized using a combination of methods, resulting in 12 experimental groups. Decellularization efficacy was assessed by quantifying remaining cells and validating the method using dsDNA quantification and staining. Collagen and sGAG contents were quantified and physico-chemical properties of the PDAC tumor microenvironment (TME) and its extracellular matrix (ECM) were characterized using histological stainings, scanning electron microscopy (SEM), mercury intrusion porosimetry (MIP), energy dispersive X-ray spectroscopy (EDX), and Fourier transform infrared spectroscopy (FTIR).

Results and Conclusions

Our results showed that sonication time and surfactant cycles had the greatest effect on eliminating the cells from the tumours. This was validated by DNA staining which allowed to quantify the number of cells in native, partially decellularized and fully decellularized PDAC samples. Total collagen and GAGs content was determined showing a slight decrease in the most soluble components, as membrane associated GAGs and recently synthesized, not crosslinked collagen.

In terms of physical properties, our SEM and MIP results showed that eliminating the cells released residual or accumulated stresses from the TME, thereby opening the porous tECM network and increasing permeability to liquids, which would make the tumour more permeable to infused drugs, large molecules, macromolecules, and cells used as therapeutic or delivery agents. The comprehensive characterization of the TME provides a foundation for developing novel interventions that could significantly enhance patient outcomes in this challenging malignancy.

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