Physico-chemical characterization of the tumor microenvironment in patient-derived xenograft models of Pancreatic Ductal Adenocarcinoma.

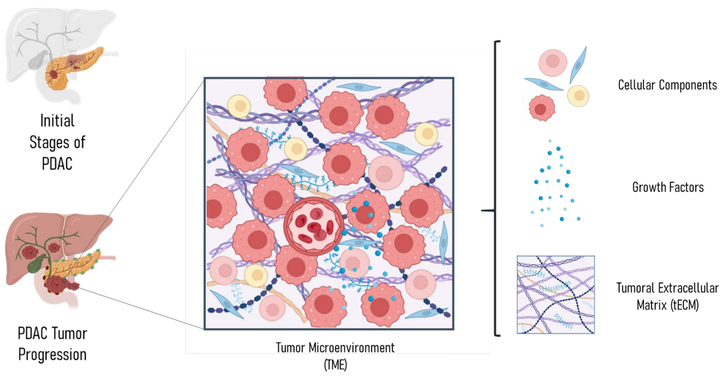
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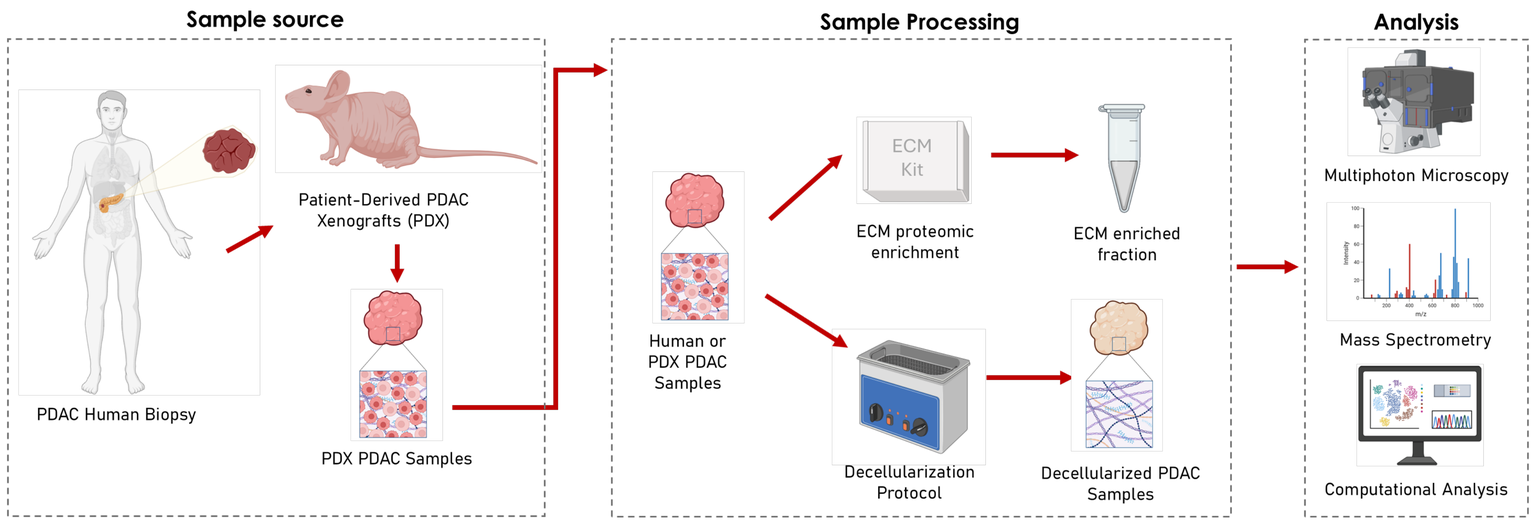
Introduction

- **Pancreatic ductal adenocarcinoma (PDAC)** is the most prevalent and aggressive form among all pancreatic cancer types.
- **Limited response** to conventional clinical treatments, which include **chemotherapy**, **surgery** and **radiotherapy**.
- Focus of research has shifted to **elucidate** the **role of tumor microenvironment** (TME) in **tumor progression and therapeutic resistance.**



Aim and Experimental Design

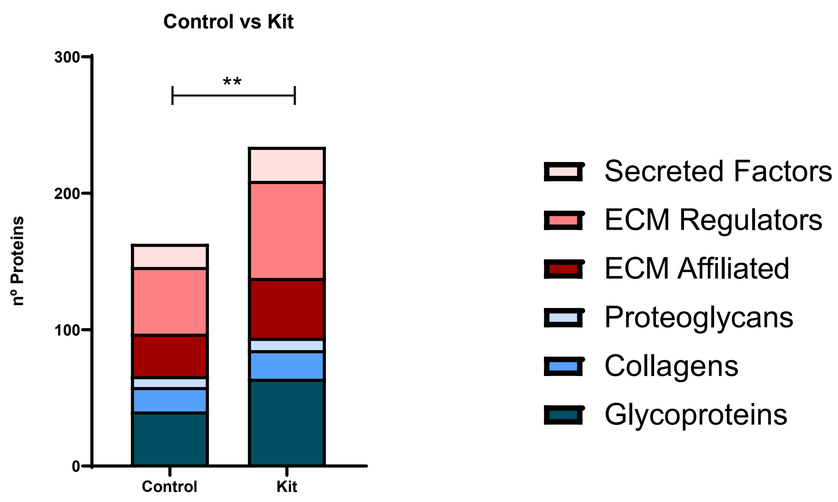
The **aim** of this study is to **characterize the PDAC tumor microenvironment** in terms of **composition** and **structure** to elucidate **new therapeutic** targets **for the treatment of PDAC**. To this end we used **patient-derived xenografts** (PDX) as models to analyze the TME and determine potential qualitative and quantitative differences between different tumor phenotypes.



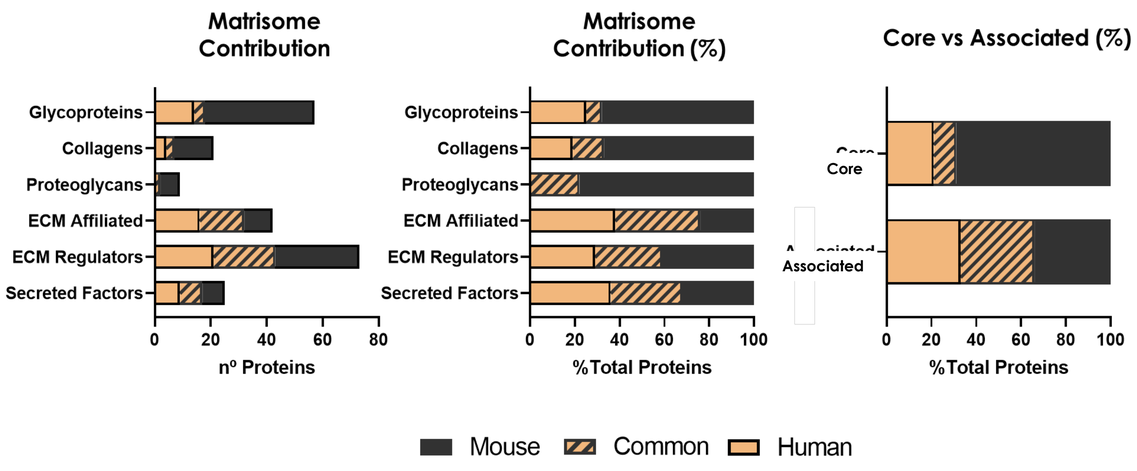
Results

PDX samples

The use of a commercial **ECM protein enrichment kit** significantly **increased the total number of ECM proteins detected** by mass spectrometry, while **no substantial changes** were observed in the **relative composition** between the **main ECM subgroups** compared to the controls.

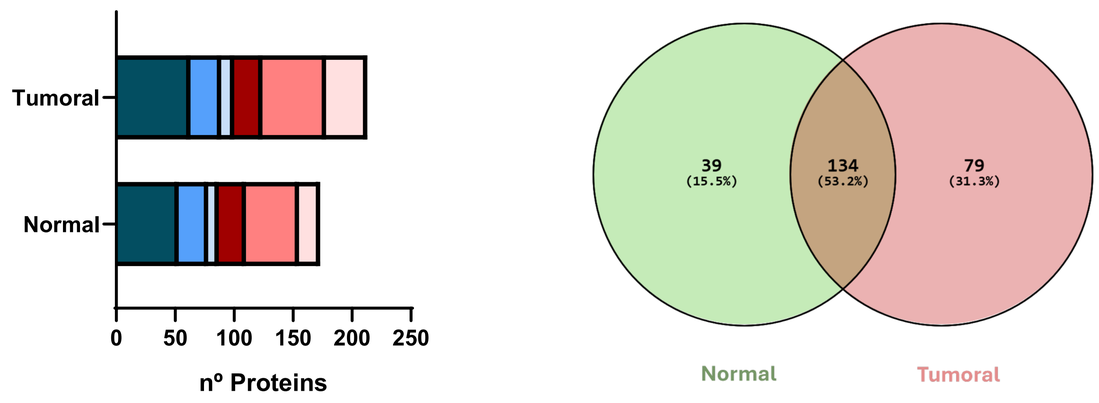


Species-specific analysis in patient derived xenograft tumors revealed that **host (mouse) cells** are responsible for **the majority of extracellular matrix production**, particularly contributing to the structural core of the ECM, which includes collagens, glycoproteins and proteoglycans.

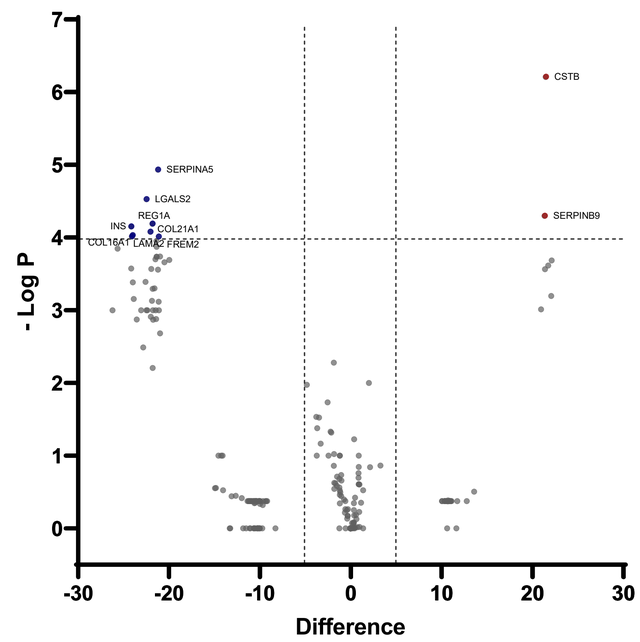


Human PDAC samples

Qualitative analysis of human PDAC samples **revealed differences in the relative composition of main ECM protein subgroups** between tumor and healthy tissue, as well as **distinct sets of proteins unique to each condition**.



Quantitative analysis identified differentially expressed proteins ($p < 0.05$), with **notable downregulation of epithelial integrity components** such as FREM1 and LAMA2, suggesting **epithelial-to-mesenchymal transition** in tumor cells. On the other hand, **upregulation of protease inhibitors** such as CTSB and SERPINB9 may **contribute** to a **denser and more fibrotic extracellular environment** by limiting ECM degradation.



Underexpressed		Overexpressed	
SERPINA5	ECM Regulators	CTSB	ECM Regulators
LGALS2	ECM Affiliated	SERPINB9	ECM Regulators
REG1A	ECM Affiliated		
INS	Secreted Factors		
COL21A1	Collagens		
LAMA2	Glycoproteins		
FREM	ECM Affiliated		
COL16A1	Collagens		

Conclusions

- **ECM enrichment boosts proteomic depth** without biasing subgroup composition, enabling a more robust characterization of the tumor matrisome.
- In PDX PDAC models, **host (mouse) cells dominate ECM deposition**, underscoring the critical role of native fibroblasts in tumor progression.
- **Human PDAC samples exhibit pronounced ECM remodeling**, marked by loss of epithelial markers (FREM1, LAMA2) and increased protease inhibitors (CTSB, SERPINB9), consistent with EMT and a fibrotic, dense microenvironment.
- Overall, our findings highlight that **deep characterization of the PDAC tumor microenvironment is essential** for the development of more effective therapeutic strategies.

References

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