Sema3A RNA nanodelivery to pancreatic ductal adenocarcinoma microenvironment for the activation of tumor immune response

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Abstract:

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive cancer with dismal survival rates. PDAC exhibit an immunosuppressive tumor microenvironment (TME) and an abnormal vasculature, limiting the efficacy of standard therapies. Semaphorin 3A (Sema3A) has shown promising preclinical results in normalizing the vasculature and activating CD8+ T cells in the TME, thereby enhancing anti-PDAC immune responses.

Here, we aim to develop lipid nanoparticles (LNPs) encapsulating the Sema3A mRNA and test their impact on PDAC progression in preclinical vascularized 3D tumor culture models and in a genetically engineered mouse model (GEMM) of PDAC.

Mut-Sema3A mRNA was successfully expressed in both endothelial and PDAC cell lines, and its translation and secretion were confirmed by ELISA and western blot analyses. Transfection with standard LNP formulations encapsulating a reporter mRNA allowed us to refine the synthesis and delivery protocols, enabling the development of mut-Sema3A mRNA-LNP.

We have set up an advanced in vitro vascularized PDAC-on-a-chip model that will be utilized to optimize and study the transcytosis of these LNPs and evaluating its effects on the TME. This model is designed to mimic the complexity of the TME through a co-culture system comprising endothelial cells, immune cells ($CD8^+$ T cells), and PDAC spheroids, providing a controlled environment to study interactions between tumor and various TME cell types.

By integrating advanced nanotherapy with a pathologically relevant in vitro model, this project aims to overcome resistance mechanisms in PDAC, offering new opportunities to improve therapeutic outcomes for patients.