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Topic: Cancer
Subtopic: Cancer models

TERMIS25_1237 - Development of a model of fibrotic tumor microenvironment and its druggability using a chick chorioallantoic membrane model integrated with a millifluidic chamber

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Introduction/Objectives

Breast cancer chemotherapy treatment faces significant challenges due to the tumor microenvironment (TME) stiffening caused by fibrosis, which progressively barriers drug diffusion. The chorioallantoic membrane (CAM) assay can be a valuable model to address this problem. By implanting in the CAM several microscaffolds fabricated using two-photon polymerization (2PP) and seeded with breast cancer cells, we want to induce a fibrotic response that mimics a fibrotic TME. The scaffolds can be fabricated on poly(dimethyl-siloxane) (PDMS) membrane that is oxygen permeable. Once inserted in a flow chamber and interfaced to the CAM model, the membrane permeability will enable precise in situ delivery of O2 and anticancer drugs. In this work, we investigate the feasibility of fabricating the microscaffolds on an implantable oxygen-permeable membrane made of biocompatible PDMS. We also predict theoretically O2 diffusion and delivery of an anticancer drug (doxorubicin) to the fibrotic TME models, through the PDMS membrane.

Methods

We developed a microfabricated PDMS membrane by first applying a layer of poly(acrylic acid) (PAA) onto a previously plasma-cleaned 25-cm2 Si-wafer via spin-coating (4000rpm, 30s), as to realize a 0.5-µm-thick "sacrificial layer". Subsequently, we deposited a PDMS layer by spin-coating (1000rpm, 30s) to achieve a 100-µm-thick membrane. Subsequently, we fabricated a pre-validated 3D microscaffold [1] (180x180x80µm³) via 2PP atop the PDMS layer. The resulting microstructured membrane was then immersed in dH2O overnight to facilitate detachment from the wafer. To predict the delivery of oxygen and

doxorubicin to the CAM, we set-up an in silico model of the millifluidic chamber, based on computational fluid dynamics (CFD).

Results

The use of a sacrificial layer enabled a gentle release of the microfabricated PDMS membrane from the Si-wafer, essential for preventing stress during the membrane transfer and therefore ensuring the stability of the microscaffolds. CFD simulations predicted that drug administration with an inlet flow rate of 0.5mL/min and a concentration of 0.05mg/mL, allowed 2ng/min of drug to diffuse through the PDMS membrane, reaching the CAM at the TME site. The concentration of oxygen decreased by less than 10% across the PDMS membrane, from the fluidic channel to the CAM, ensuring minimal impact on oxygen availability at the site of the TME.

Conclusions

Our findings indicate a breakthrough in methods for targeted drug delivery in CAM studies, a notable enhancement compared to traditional methods [2]. Previous studies administered anticancer drug, as doxorubicin, broadly, topically or intravenously, causing diffuse and non-targeted effects. Our approach not only facilitates oxygen distribution to the CAM but also enables control of drug administration to localized areas of interest, such as the model of fibrotic TME developed here. These findings are crucial for discovering new drug combinations, for example coupling chemotherapeutics with anti-fibrotics, and for optimizing drug administration protocols to enhance therapeutic outcomes.

References

1. Conci C et al., 2022, DOI: 10.1002/adom.202101103
2. Ribatti D., 2016, DOI: 10.1016/j.mod.2016.05.003

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