MICROBIOME ON CHIP (MOC): A NOVEL MULTI-ORGAN PLATFORM FOR PERSONALIZED THERAPY IN CANCER

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Introduction

It is now evident that the gastrointestinal bacteria contribute in shaping the immune system, the etiopathology of cancer and therapy responses [1-2].
In vitro traditional models lack the cellular complexity and physiological architecture present in the human intestine [3-4]. On the other hand, *in vivo* systems often fail to recapitulate results obtained in human and they are limited by poor experimental control.
3D-microfluidic culture systems may overcome these limitations, because they recreate complex multicellular architectures in a finely controlled dynamic environment [4-6].

Methods

A novel microfluidic platform that integrates 3D models of the human intestine, the systemic vasculature and the tumor microenvironment (TME) was developed using soft lithography techniques.
The microbiome-on-chip (MOC) is composed by two modules. The first module consists of a 3D gut-on-chip composed by an epithelial compartment and a vascular one separated by a collagen-based gel. Physiologically relevant luminal flow and peristalsis-like mechanical deformations are applied on the device thanks to an innovative technology recently developed in the lab.
The second module is designed to culture 3D tumor spheroids and test different therapeutic strategies on patient-derived tissue. The whole system allows real-time multiparametric monitoring and could be used as a predictive model to promote patient-specific therapies and improve antitumor responses

Results

The following preliminary results were obtained using single-module devices while the complete platform is currently being developed and tested to study the effect of microbiota on tumor microenvironment and therapeutic responses.

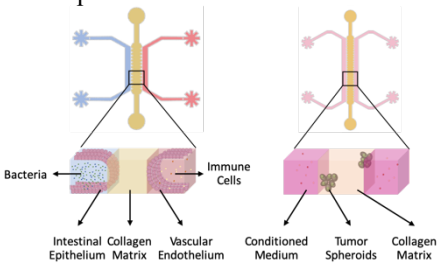

Figure 1: Intestinal and Tumor microfluidic models

The proposed intestinal model allows to obtain a 3D complete and functional intestinal epithelium in 5-7 days of culture (Figure 2A). Epithelium integrity and functionality was assessed using 4.4KDa TRITC-Dextran.
Mucosal samples from patients' intestinal resections were co-cultured on the device to evaluate the influence of tumor-associated microenvironment on intestinal integrity.
Patient-derived tumor spheroids were cultured in the tumor-on-chip module for 4-5 days and different therapeutic strategies were tested. Both tumor and immune cells were successfully maintained on the device.

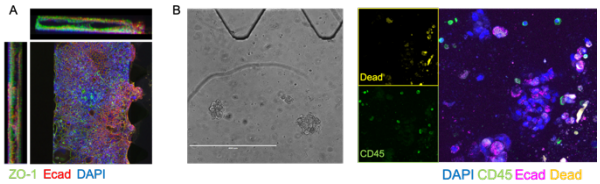

Figure 2: (A) Confocal microscopy image of a complete 3D epithelium stained for tight junctions (ZO-1), E-cadherin (Ecad) and nuclei (DAPI). (B) Tumor spheroids composed by both tumor (Ecad) and immune (CD45) cells.

Discussion

The shear stress and the mechanical deformations applied on the device can increase the ability of cells to create a complete intestinal epithelium. Different culture conditions must be tested to find the proper stimulation parameters.
The use of patient-derived tumor spheroids can promote personalized therapy; however, the proposed tumor model is also suitable to identify universal features that could be manipulated to improve antitumor responses in different tumor types.

References

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