A 3D mechanically-active gut-on-chip enables prediction of response of melanoma to immune checkpoint inhibitors based on fecal microbiome

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Immune checkpoint inhibitors (ICI), have delivered unprecedented and enduring outcomes in the treatment of various cancers, with notable efficacy observed, particularly in melanoma cases [1-2]. However, the response to ICI remains heterogeneous [3] and can be influenced by several environmental factors, including the gut microbiome [4-5]. Although animal models have been extensively employed to study microbiome-host molecular interactions, the existing limitations, such as interspecies differences and the absence of a fast, robust, and accessible experimental model, pose significant challenges in efficiently stratifying patients based on response and implementing therapeutic manipulation of the microbiome [6].

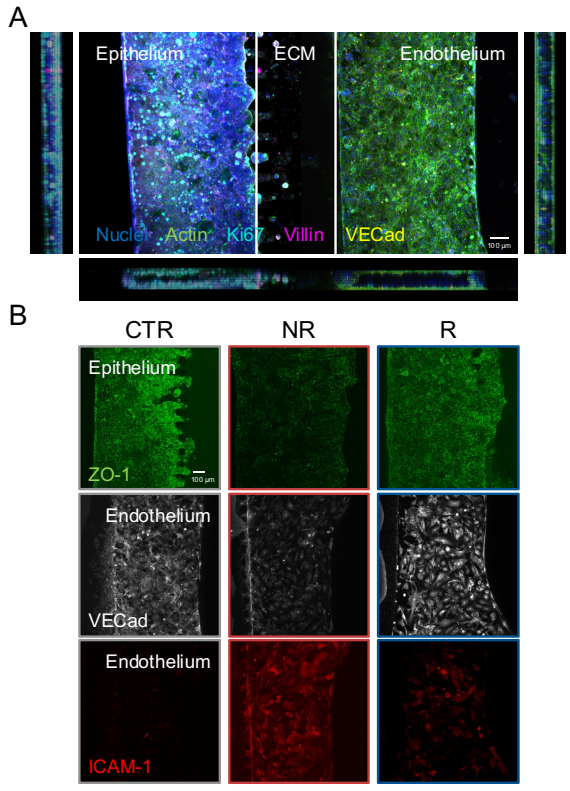

Figure 1 *A) Confocal characterization of Gut-on-chip device. B) Effect of fecal microbiota from responder (R) and non-responder (NR) patients on intestinal barriers.*

In this context, we present a 3D microfluidic-based device modelling gut epithelial-endothelial barriers and featuring peristaltic-like movements, with the aim to use it as a reliable method to predict the clinical outcome of ICI therapy through fecal microbiota's testing. The model is composed by epithelial and endothelial 3D tubular structures separated by extracellular matrix (ECM) with a superimposed actuation chamber able to generate controlled peristaltic-like movements. The geometry of the platform enables the manipulation of both epithelial and endothelial compartments while promoting interactions between different components. After characterizing the architecture and functionality of our model using markers of integrity (Actin, VE-cadherin), maturation (Villin) and proliferation (Ki-67), we assessed the ability of our platform to recapitulate biologically-relevant aspects of the interactions between intestinal epithelium and microbiota. In particular, we exposed our Gut-on-Chip device to fecal microbiota of patients with melanoma responsive (R) or non-responsive (NR) to immunotherapy and observed their specific effects on the intestine. Fecal microbiota from R patients did not alter the integrity of the intestinal barrier (ZO-1, E-cadherin, B-catenin), while we observed a disruptive effect of NR microbiota on both the epithelium and the endothelium coupled with endothelial cells activation (ICAM-1), suggesting acute inflammation. Thanks to the application of multiOMIC approaches, we also investigated the molecular mechanisms underlying the specific responses of the intestinal epithelium to fecal microbiome and the potential therapeutic effect of fecal samples from melanoma patients responding to immunotherapy which were able to mitigate the inflammation caused by NR microbiota.

Our study provides compelling evidence of the model's biological relevance compared to mice and conducts detailed mechanistic investigations, unveiling epithelium-specific biomarkers and microbial factors correlating with clinical outcomes in melanoma patients. These findings may serve as targets for future prognostic testing and therapeutic interventions.

References

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