Integrating Immunological Aspects into a Multi-Organ-Chip Platform

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Abstract

During the last decade organ-on-a-chip technologies received increasing attention in the scientific community. The idea of combining different tissue types on a physiological-like system creates completely new options on how substances can be characterized without the use of animal experiments. The Multi-Organ-Chip platform is designed to combine different human cell and tissue types like 3D-spheroids, barrier models or biopsies in one microfluidic system. A peristaltic on-chip micropump enables circulation of medium, allowing for a constant perfusion between the compartments. Here we present the cultivation of primary, monocyte-derived dendritic cells on our microfluidic system alone and together with human dermal microvascular endothelial cells (HDMEC) or human epidermis models. For analysis we measured the typical activation marker CD86 and the vitality of the dendritic cells by flow cytometry. Functionally different sensitizers were selected to investigate their effects in our model.

Experimental Setup

Cultivation of primary dendritic cells in the 2-Organ-Chip

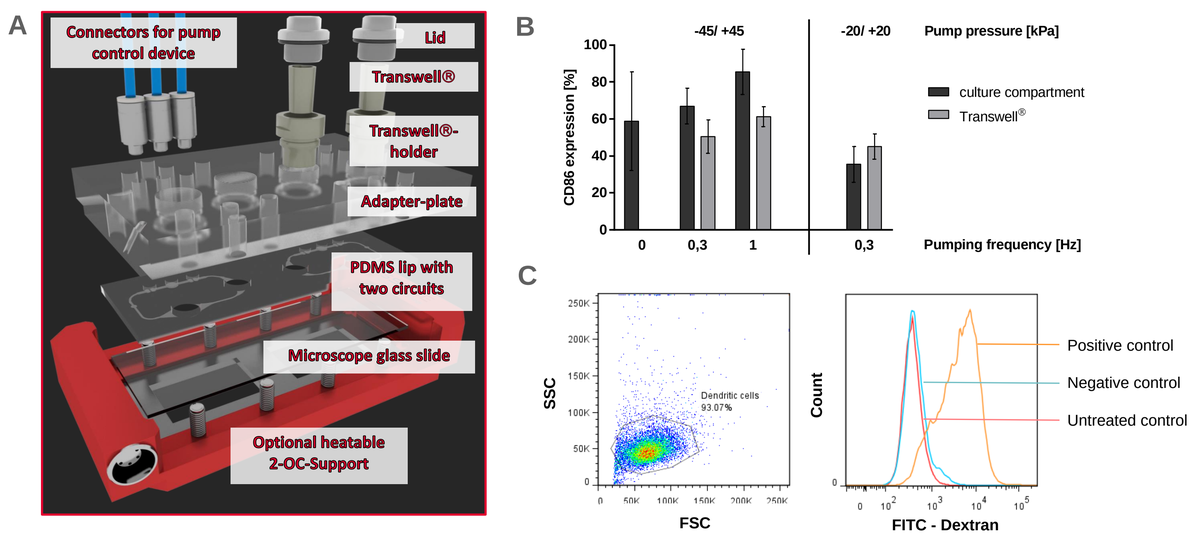


Fig.1 (A) Composition of the 2-Organ-Chip at a glance. (B) Activation of dendritic cells based on the induction of co-stimulatory molecule CD86, examined factors: culture compartment cultivation, Transwell® cultivation, pump pressure and pumping frequency. (C) FITC-Dextran endocytosis assay of dendritic cells after 24 h 2-Organ-Chip Transwell® cultivation together with EpiDerm™ models under perfused conditions.

Cocultivation of immature dendritic cells with HDMECs

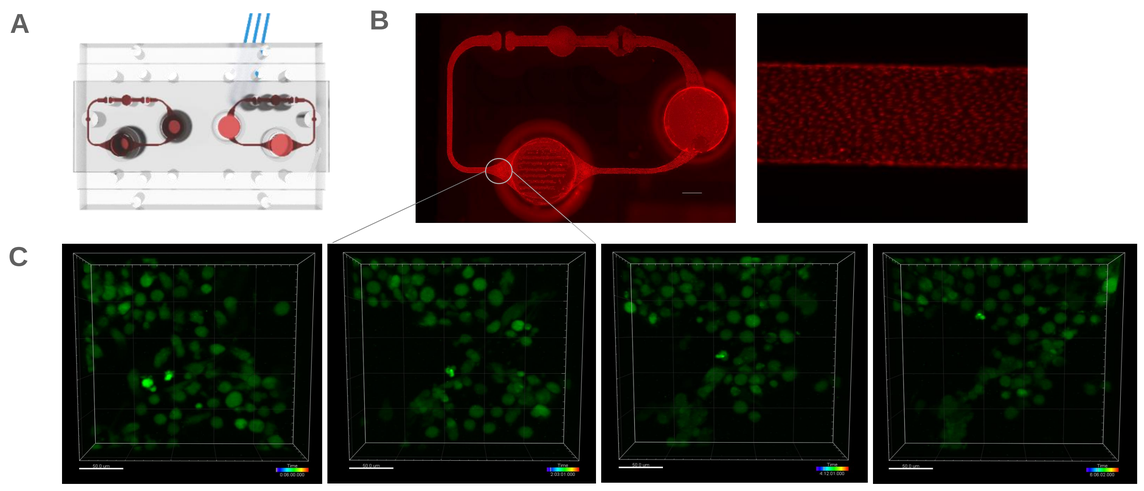


Fig. 2 (A) Bottom view of the microfluidic channels of the 2-OC. (B) Confluent cultivation of the microfluidic channels with HDMECs after 7 days of dynamic culture. To represent live cell viability calcein red-orange AM assay (red) was performed. Scale bar: 2mm. (C) Time lapse of dendritic cells cocultured with endothelial cells in the 2-Organ-Chip under static conditions captured by 2-Photon microscopy over 18 h. For detection of movement of the dendritic cells z-stacks were created every 3 minutes (here presented every two hours (0h- 2h-4h- 6h). Dendritic cells were visualized by CellTracker™ Green (10 µM) staining.

Cocultivation of immature dendritic cells with human epidermis

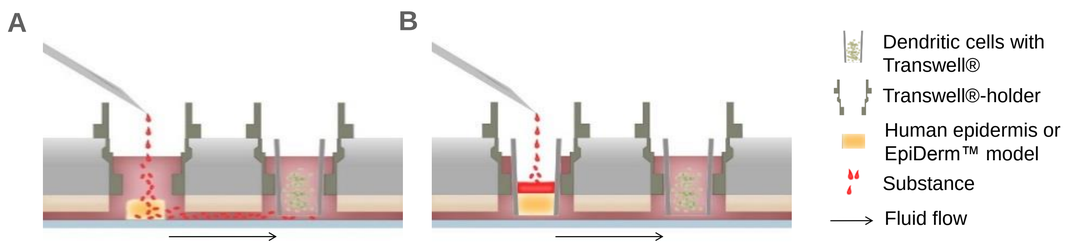
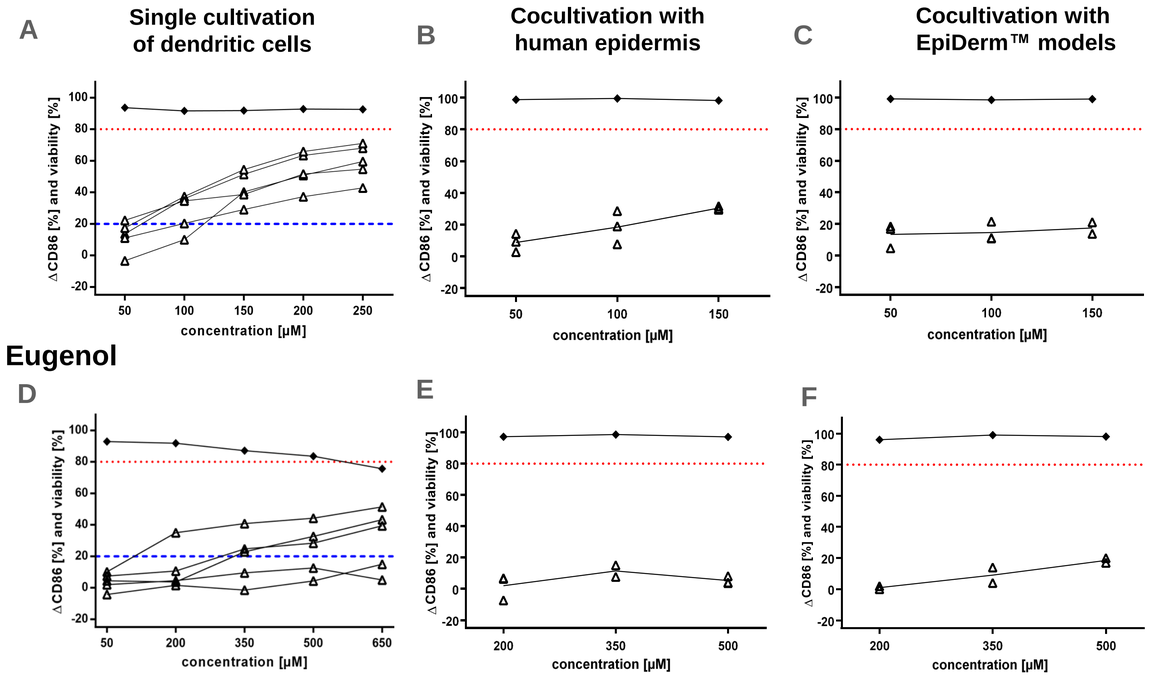


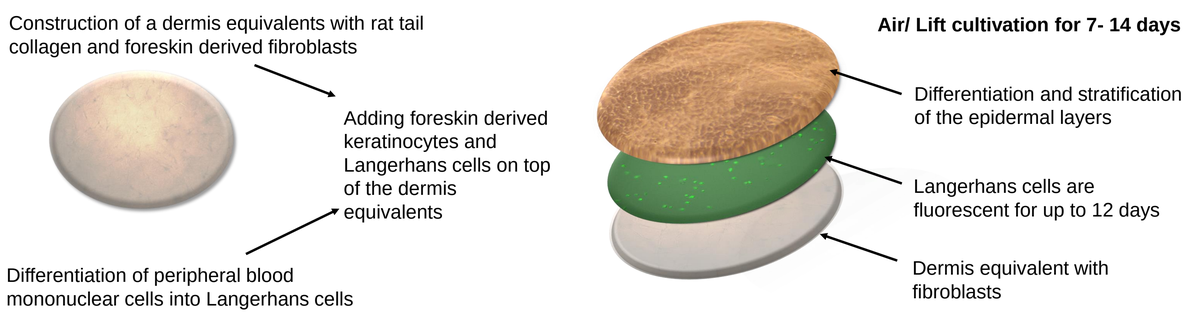
Fig. 3 *Ex vivo* human epidermis (A) or MatTek EpiDerm™ models (B) and immature dendritic cells were cultivated in separate culture compartments connected by the microfluidic channels for 48 h under perfused conditions. The effects of substance application were comparatively analyzed after systemically application and topical application onto EpiDerm™ models.

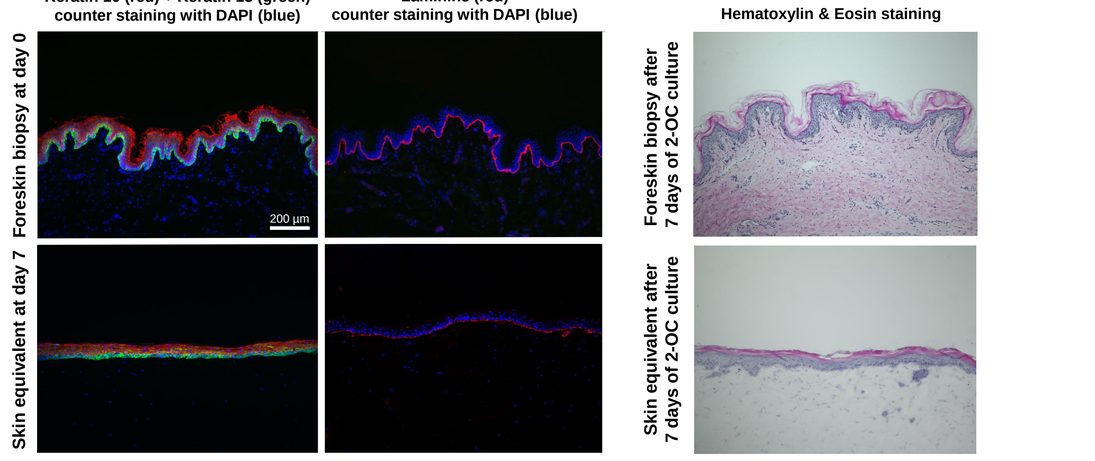
Fig. 4 Response of dendritic cells to sensitizers represented by calculation of ΔCD86 induction. (A and D) Data of static PBMDC sensitization assays (single cultivation of dendritic cells) provided by Beiersdorf AG. Each triangle indicates a single measurement from cells of a single donor. Associated cell viability is indicated by dotted lines (red) and threshold for characterization as sensitizer is indicated by dashed lines (blue). (B and E) 2-Organ-Chip-based perfused assays using human epidermis and pooled donor cells. (C and F) 2-Organ-Chip-based perfused assays using EpiDerm™ models and pooled donor cells.



Next challenge - Integration of Langerhans cells into skin models

New experiments are ongoing to build an immune competent skin model with integrated CellTracker™ Green stained Langerhans cells.





Results and Discussion

Our data show a strong influence of pump pressure and pumping frequency on the activation of dendritic cells. Hence, we established an adequate set up by cultivating the dendritic cells in cell culture inserts, preventing cell activation due to shear stress. Compared to existing sensitization assays, the main advantage of the presented cocultivation is the presence of an epidermis equivalent, partially integrating important parameters such as metabolism and skin barrier function. Currently, an adequate medium composition for the co-cultivation is under investigation to avoid the high expression values of CD86 in the control groups and to improve the vitality of the skin models.

The use of immunocompetent skin models would be a further enhancement of the current setup. Therefore the integration of Langerhans cells into skin models is addressed in ongoing experiments. Next steps will also focus on the cultivation of a 3D matrix including different immunological cell types to characterize the formation of immune-competent micro-organoid structures within the 2-Organ-Chip.
This will be a promising enhancement to integrate immunological reactions on further multi-organ combinations.

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