Cancer-on-chip: modelization of the human brain vasculature in tumoral context

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The blood-brain barrier (BBB), a physiological barrier between the blood flow and the central nervous system (CNS), regulates the influx of substances into the brain, to maintain neural homeostasis. However, this selective permeability can hamper the pharmacological development of new therapeutics due to complexities in predicting pharmacokinetic and dynamic behaviors. *In vivo* BBB models lack of accuracy in representing human physiology due to interspecies differences, leading to a critical need for advanced humanized *in vitro* BBB models in healthy or pathological conditions such as a tumoral context [(1)]. Recent developments in microphysiological systems (MPS) have opened the path to better modeling of brain vasculature [(2)].

The first step of this study focuses on the design, mold printing and casting of a glass-PDMS (polydimethylsiloxane) microchip. This chip hosts a hydrogel mimicking the brain extra-cellular matrix, casted around a 200 µm diameter needle. The needle is removed after gelation to obtain a hollow channel modeling a venule. Gelation issues of the collagen-fibrin-based hydrogels led to investigate changes in collagen I microfibers processing. For a physiologically relevant model, 3 types of human cells were used: endothelial cells (HBEC-5i) to mimic the walls of a venule, pericytes (PC) that should have a major angiogenic role, and astrocytes (HA) whose feet should reinforce the vasculature in formation. In addition, glioblastoma cells may be added to model a tumoral microenvironment. After having conducted 2D tests to determine the appropriate medium and cell proportions for the healthy coculture, cancer cells in different ratios were added, to model early and late stage of tumoral development. The next steps will consist in the mechanical characterization of the hydrogel and its effect on cell behavior (proliferation, migration...), and perfusing the system to reproduce *in vivo* blood flow and to promote angiogenesis.

The current and future advancements in chip design, cell coculture conditions, physio-chemical characterization of the appropriate hydrogel and blood flow modeling in this BBB-MPS hold promise for development of therapeutics, particularly for central nervous system disorders, leading to more effective personalized medical solutions.

References :

[(1)] Piantino, et al. “Three-Dimensional in Vitro Models of Healthy and Tumor Brain Microvasculature for Drug and Toxicity Screening” Frontiers in Toxicology, 2021, doi: 10.3389/ftox.2021.656254

[(2)] Nakayama-Kitamura et al. “Collagen I Microfiber Promote Brain Capillary Network Formation in 3D Blood-Brain Barrier-Microphysiological Systems” Preprints, 2024, doi: 10.20944/preprints202409.2209.v1

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