A Microfluidic Blood-Brain Barrier Model for Studying Monocyte-Mediated Oncolytic Virus Delivery to Glioblastoma

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The development of physiologically relevant in vitro models is essential for advancing drug delivery strategies targeting the central nervous system (CNS)[1]. Among these, the blood-brain barrier (BBB) poses a significant challenge due to its selective permeability and complex cellular architecture[2]. In this work, we present a multicompartment microfluidic BBB-on-chip platform designed to replicate key structural and functional features of the human BBB, enabling the investigation of therapeutic delivery mechanisms across the barrier to a target site. The first two compartments constitute the BBB mimic and consist of two parallel microchannels separated by a porous polyethylene terephthalate (PETE) membrane, fabricated via soft lithography and bonded using oxygen plasma. The third is the target compartment, fluidically connected to the BBB and housing the desired tissue model. Human umbilical vein endothelial cells (HUVECs) are cultured on the upper channel to mimic the luminal side of the BBB, while human astrocytes and pericytes are co-cultured on the lower side to simulate the abluminal interface. The chip supports long-term co-culture (up to 10 days) under dynamic conditions, maintaining high cell viability and stable barrier function. The integrity and physiological relevance of the BBB model were validated through transendothelial electrical resistance (TEER) measurements, permeability assays, and immunofluorescence staining of key markers, including CD31, ZO-1, and GFAP. Our device is validated for a cell-based therapeutic delivery strategy for glioblastoma (GBM), an aggressive brain malignancy with poor prognosis and limited treatment options. Specifically, we prove the potential of monocytes, pre-loaded with herpes simplex virus type 1 (HSV-1)-based oncolytic viruses (OVs), to act as carriers for targeted delivery to the tumor compartment. Monocytes are perfused through the upper channel of the BBB-on-chip and monitored for their ability to transmigrate and transfer viral particles to GBM spheroids in the downstream compartment. Our results show that the engineered BBB model accurately simulates key aspects of the human barrier and enables real-time observation of immune cell trafficking and virus-tumor interactions. OV-loaded monocytes successfully cross the barrier and infect GBM spheroids, supporting the feasibility of this therapeutic strategy. This work combines microfluidic technology with cell-based therapies and can be easily adapted to different CNS diseases, providing an invaluable tool for studying their mechanisms and novel therapeutic approaches.

Keywords: BBB-on-a-chip, Glioblastoma, oncolytic virus, monocyte delivery, drug delivery

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