DEVELOPMENT OF A THREE-DIMENSIONAL BRAIN-ON-A-CHIP WITH AN INTERSTITIAL LEVEL OF FLOW AND ITS APPLICATION AS AN IN VITRO MODEL OF ALZHEIMER’S DISEASE

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ABSTRACT

In vitro models for neurologic diseases have been highly demanded for better understanding of pathology and strategies for treatment of the diseases such as Alzheimer’s disease (AD); however, there have been limits in mimicking in vivo microenvironment on in vitro system. Here, we have developed a microfluidic chip based on three-dimensional (3D) neurospheroids providing interstitial level of flow mimicking in vivo microenvironment more closely. With this platform, we investigated the effect of flow on neurospheroids in size, neural networking, and neural differentiation. Also, we observed the effect of amyloid-β (Aβ) which is generally accepted as a major component causing AD.

KEYWORDS: Brain-on-a-chip, Neurospheroid, Interstitial flow, Alzheimer’s disease

INTRODUCTION

Recently, 3D culture1, which provides cell-cell contacts and interactions that are essential features of 3D brain tissue, and interstitial fluid flow2, which serves the critical function of delivering nutrients and clearing metabolic wastes through the brain tissue, have been applied to in vitro studies of AD, separately. Here, we developed an in vivo-mimicking microfluidic 3D brain model with an interstitial level of flow by combining concave microwell arrays with an osmotic micropump system.

EXPERIMENTAL

We developed an in vivo-mimicking microfluidic 3D brain model with an interstitial level of flow by combining concave microwell arrays with an osmotic micropump system (Figure 1).

Figure 1: Schematic diagram of a three-dimensional brain-on-a-chip with an interstitial level of flow. The chip contains concave microwell array for 3D culture and the osmotic micropump system for a continuous flow of medium at the level of interstitial flow. By providing a 3D cytoarchitecture and interstitial flow, this chip approximates the microenvironment of normal and AD brains, facilitating the investigation of Aβ effects on 3D neural tissue.

Using this brain model, we investigated the effect of flow on 3D micro-spheroidal neural tissue (neurospheroids). The flow provided by the osmotic micropump system was about 0.25 μL/min, comparable to the level of interstitial flow. To investigate flow effects, we prepared two types of brain model: a static model (neurospheroids cultured without flow, Group I) and a dynamic model.
(neurospheroids cultured with flow, Group II). Changes in neurosphere size and neural network formation between neurospheroids were investigated in both static and dynamic models. To demonstrate the potential of this system as an in vitro brain model for neurologic disease studies, we performed the first test of the effects of Aβ on 3D neurospheroids cultured with interstitial flow in vitro. By culturing neurospheroids in parallel with and without Aβ, we were able to mimic the normal and Alzheimer’s disease brain simultaneously on a single platform.

RESULTS AND DISCUSSION

To determine the effects of an interstitial level of flow on neurospheroids, we cultured neurospheroids in two different model systems: Group I and Group II. The size of neurospheroids in Group II was larger in general and it slightly increased, whereas that of Group I essentially unchanged (Figure 2(a)). We next examined the formation of neural networks by optical and SEM imaging and Group II showed greater neurite extension leading to more robust neural network formation (Figure 2(b)).

Figure 2: The effects of an interstitial level of flow and Aβ on neurospheroids. (a) Size distribution analysis of neurospheroids of Group I and group II over time. (b) SEM and optical images of neural network in Group I and Group II. White arrows indicate neurites. (c) Immunofluorescent images of neurospheroids against synapsin IIa and β-III tubulin and their intensity comparison graphs.

To study how Aβ affects neurospheroids, we cultured spheroids in the presence of Aβ under static conditions (Group IA) and dynamic conditions (Group IIA) as well. Lower intensity of synapsin IIa (synapse marker) and β-III tubulin (neurite marker) in immunofluorescent images of Group IA and Group IIA comparing to control groups (Group I and Group II) indicates neurotoxic effects of Aβ that leads to neural destruction and synaptic dysfunction (Figure 2(c)).

CONCLUSION

Using a biomimetic approach, we developed a brain-on-a-chip that creates 3D cytoarchitecture and interstitial flow. The in vivo-like microenvironment provided by this 3D culture-based microfluidic chip has great potential as an in vitro brain model. As such, this platform could fill the gap between traditional in vitro neural cell culture models and in vivo brain studies, serving as a more reliable tool for studying neurological disease pathology and treatment strategies as well as drug screening applications.

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