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Three-Dimensional Microfluidic Platform with Neural Organoids: Model System for Unraveling Synapses

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ABSTRACT: Unraveling the large number of various signals in the brain under the influence of physical and chemical cues that govern the formation of individual neurons, axons, dendrites, and their functional synapses during the development of neural network is a challenging task. To understand this task, microfluidic devices equipped with microchannels for reconstitution of cell/tissue-culture environments have been studied. Microfluidic devices are emerging as powerful tools in neurobiology, since they are capable of controlling and manipulating the microenvironment of the brain in a precise manner. They can enhance the physiological relevance of three-dimensional (3D) cell culture by allowing spatial control over fluids in micrometer-sized channels. Recent technological advancement in designing microfluidic platforms for studying neural communication, disease progression, and detection of neurotransmitters enhance our fundamental knowledge and understanding. However, more such advanced and innovative interventions are required. This Viewpoint focuses on highlighting a few of them with future scope of further advancement in this field.

KEYWORDS: *Microfluidic device, neural organoid, synapse, neurotransmitters, 3D cell culture*

Understanding the function and dynamics of the brain is an exciting field of research due to its highly complex and sophisticated networks, which is still considered to be similar to a locked black box. Unraveling this extremely complex machinery requires innovative strategies, which can mimic the physical environment of the brain as well as offer multimodal efficient structural and functional components to study and reconstitute the miniature of Brain Organoid-On Chip. Early development of the brain originates from neuroblasts that migrate and differentiate into the neurons and glia of brain parts.[1] During this process, neuroblasts encounter an array of complex microenvironments followed by the development of neural polarity and early neural networks for communication of signals.[1] It originates various functions such as integrated network communication and regulation of metabolic, physical, and cognitive functions, which offers a better understanding of complex brain functions. Moreover, it is crucial to understand the mechanistic insights of the formation of individual neurons, axons, dendrites, and their functional synapses during the development of neural networks and a large number of various signals under the influence of physical and chemical cues. To understand this task, microfluidic devices equipped with microchannels for reconstitution of cell-culture environments with channels of micrometer-scale dimensions have been studied. Microfluidic devices are emerging as powerful tools in neurobiology, since they are capable of controlling and manipulating the microenvironment of cells in a precise manner. In this approach, the introduction of engineering technologies for solving biological questions offers the fabrication of microfluidic based systems, where one can study the function of individual brain cells as well as their circuit or network in a stable microculture system in a laboratory. Recently, microfluidic based systems have been explored for understanding the various neurological functions as well as reconstitution of disease models which enriched our understanding and knowledge. Here, we highlight a few recent key developments in this area as follows: Park et al. showcased an interesting model system where they reconstituted a three-dimensional (3D) human triculture system for understanding neurodegeneration and neuroinflammation in Alzheimer's disease (AD) (Figure 1).[2] They created an engineered model

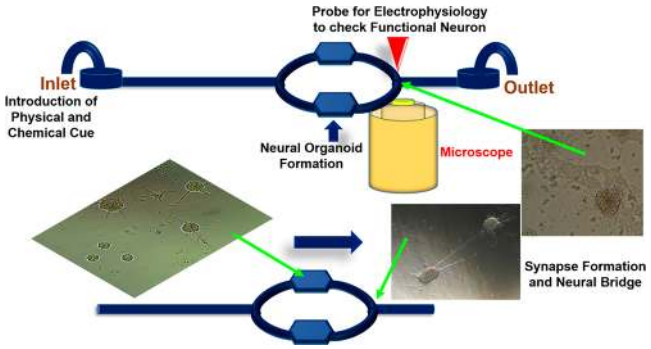

Figure 1. Cartoon represents design of 3D microfluidic platform for culture of neural organoid, real time monitoring of synapse formation and evaluation of functional neuron along with imaging.

system of neuron, astrocyte, and microglia interaction in the AD environment, which allows one to understand the recruitment of human microglia, neuroinflammatory response, and damage to neurons or astrocytes. To accomplish this model, they created a human triculture system, where neurons and astrocytes differentiated first and then adult microglia cells at different stages of AD were added. This fascinating, recently

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developed 3D human AD triculture model system demonstrated two well established Alzheimer's disease progression pathway such as Aβ aggregation and hyperphosphorylation of tau along with an elevated expression of chemokines and cytokines (CCL2, IL8, TNF-α, and IFN-γ). Their model system offers an interesting platform for the exploration of mechanistic insights of AD and screening of new therapeutic leads. Lee et al. reported how a physical cue such as optogenetic stimulation has been utilized for myelination of axons in a microfluidic platform.[3] Kundu et al. showed how topographic and chemical cues stimulate primary neurons and promote neurite growth.[4] They showed that an optimal frequency is required for extending neurites in a topographically complex environment, which establishes prominent directional selectivity. Additionally, they showed that this cue synergistically increases attractive and suppresses repulsive guidance using a chemical cue Netrin-1, followed by elimination of repulsive guidance by a chemorepellent Semaphorin3A. These findings conclude that topographic cues play an important role in neural signaling processes.[4] Li et al. reconstituted neural networks between superior cervical ganglion (SCG) neurons and their effector smooth muscle cells (SMC) in a microfluidic platform. This interesting reconstituted platform is capable of detecting amperometric levels of individual neurotransmitter released inside the active SCG-SMC synapse junction using carbon fiber nanoelectrodes and recording postsynaptic potential using glass nanopipette electrodes. This reconstituted on-chip microfluidic platform creates an in vivo environment where one can monitor chemical synaptic transmission in real time and may find new mechanistic insights of neuronal communications.[5] Although considerable attempts have been made to develop reconstituted model systems for understanding neural function, our understanding in this field is still limited and requires more such disruptive interventions in this field. In this direction, we are involved in designing an advanced prototype based microfluidic system for neuronal organoid culture, monitoring the synapse formation, and following with quantification of neurotransmitters.

In summary, the brain is an extremely complex machinery. Unraveling its structure and function required innovative strategy, which can mimic the physical environment of the brain as well as offer multimodal structural and functional components to study and reconstitute the miniature of the brain or neuro-organoid-on chip. The above discussed platforms will not only help to reconstitute the confined brain atmosphere, but also would be an ideal platform for development of highly reproducible brain/neuro-organoids, which can enrich our understanding of early brain development processes and disease progression. Moreover, this microplatform device can be used for various other applications such as mimicking the microenvironment of glioblastoma, high throughput screening of drugs, and identification of neurotransmitters at the early stage of brain development.

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Notes

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