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Commentary

Neural Tube Organoids: Study Model for Human Developmental Biology and Disease

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DESCRIPTION

Pluripotent Stem Cells (PSCs) have emerged as a valuable tool for basic and translational research due to their intrinsic capacity to self-renew while also maintaining the ability to differentiate into diverse cell types. Over the past decade, evolving technologies in the stem cell field have facilitated the development of advanced PSC culture systems that better support the regulation and control of *in vitro* environmental conditions, enabling not only the recreation of fundamental aspects of mammalian embryonic development but also the modeling of complex human diseases using genetically distinct induced pluripotent stem cell lines. Most notably, the use of advanced 3-Dimensional (3D) culture systems known as "organoids" has become a popular *in vitro* stem cell modality capable of recapitulating the biophysical properties and cellular organization of various organ tissues within the body through the formation of complex 3D structures [1,2]. Organoid technology has become increasingly relevant for neuroscience research, and several groups have utilized these advanced culture systems to generate the diverse cell types that exist within the regional microenvironments of the human brain with precise spatial arrangements and niche-specific cellular network interactions [3,4]. As such, these "cerebral" and "cortical" organoids have become a powerful system to model human neurological disorders that involve diverse regions of the nervous system [2,5].

Similarly, developmental biology groups interested in understanding the earliest stages of embryonic development known as gastrulation have begun to employ organoid culture techniques to generate structures termed "gastruloids," which resemble the differentiation of the post-implantation embryo including the formation of the neural tube and surrounding tissues [6-11]. Work in the gastruloid field has generated a growing interest in modeling Neural Tube Defects (NTDs), and the application of this organoid technology has supported various platforms used to investigate the genetic and environmental etiologies behind multiple developmental disorders, many of which utilize therapeutic drug screening approaches [12,13]. Spina Bifida, one of the most common NTDs, has several classifications each characterized by varying severity, degree of neural tube closure, and types of cells that are affected in the spinal cord area [14,15]. *In vitro* neural organoid models have been used to investigate the efficacy of nutritional interventions in Spina Bifida using both induced pluripotent stem cells derived directly from Spina Bifida patients [16] as well as pluripotent stem cells with chemically induced neural tube disruption [17]. However, these organoid models do not precisely represent the cellular or regional identities of the spinal cord that are most often affected in this disorder and are therefore limited in their ability to recapitulate some of the key manifestations of the disease.

Improvements to PSC-derived spinal organoids have been made over recent years, starting from homogenous populations of neuronal cells resembling an anterior neural identity and displaying a dorsal-ventral body axis arrangement [18-22] to more heterogenous neuromesodermal cell populations with caudal neural tube-like axial elongation as described here. Expanding on early developmental studies in model organisms and embryonic stem cell-derived gastruloids that examined the cell-intrinsic signaling mechanisms underlying neural tube formation and development, PSC-derived Neuromesodermal Progenitor (NMP) organoids have been faithfully and reproducibly directed in culture by extrinsic factors to pattern into the diverse lineages that reside both within and outside of the developing neural tube [22]. Already, NMP organoid models have shown to be useful in the investigation of complex neuromuscular diseases that involve diverse cell type interactions like neuromuscular junction activity [19,21].

The work presented in this article highlights a versatile platform for generating NMP organoids that both recapitulate fundamental aspects of human development and serve as a promising tool for future studies of human disease. Beginning with the dissection of the dynamic developmental signaling pathways whose interactions dictate body plan assignment and the establishment of specific cell types, this protocol efficiently and reproducibly generates organoids that contain diverse populations within the spinal cord niche such as motor neurons, neural crest-derived glia, and the adjacent sclerotome derivatives (e.g., vertebrae). When applied to a disease like Spina Bifida, one

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can establish a comprehensive model that allows for the interrogation of the cumulative, pathological effects of toxin mediated NTDs on neuronal and non-neuronal tissues alike throughout the developmental trajectory [10,18].

CONCLUSION

Although the method presented here showcases a highly efficient and reproducible method for generating a versatile stem cell-derived spinal organoid model, the authors do acknowledge the following limitations: First, this protocol does not utilize any sort of bioengineered device with matrix scaffolding or microfluidic properties that would allow for the precise control of morphogen gradient exposure to cells within the organoid in a spatially defined and restricted manner, which would create regionally distinct and separate boundaries between the rostral-caudal and dorsal-ventral axes as it occurs *in vivo*. Second, through the combined synergistic activation of the sonic hedgehog pathway this protocol biases the neuromesodermal organoids away from a dorsal character towards a ventral neural tube domain (pMN), which can be overcome by simultaneous exposure to BMP signaling to generate a greater dorsal-ventral identity. Lastly, although organoids have provided a better *in vitro* cellular model over traditional homogenous monolayer cultures, they do not fully recapitulate the complete diversity and heterogeneity of cell types that exist within regions of the body, nor do they contain cerebrospinal fluid or established vasculature. Regardless, pluripotent stem-cell derived organoids such as the one described in this article provide a complementary model system through which scientists can better study complex mammalian development and human disease.

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