Molecules and Cells

Editorial

Special Issues on Neurobiology: From Gene, Network to Behavior

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https://doi.org/10.14348/molcells.2022.2047
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For over a century, the "neuron doctrine" in which the neuron is the structural and functional unit of the nervous system, and neurons are communicated through "synapse", a specialized region between neurons, has provided a conceptual foundation for modern neurobiology (or neuroscience). We all witnessed that remarkable progress has been made in the variety of disciplines in neurobiology, ranging from neurodevelopment to neural correlates of behavior. This progress has been, in part, driven by the advancement of state-of-the-art, innovative neurotools, such as many molecular, cellular technologies, high-throughput genomic sequencing, patch-clamping electrophysiology, and imaging technologies during the last century. To review the current special issues in neurobiology, five minireviews are invited from prominent investigators who have recently published interesting findings with novel neurotools.

The first review article by Lee and Sun (2022) deals with neural organoid, a versatile model for neurobiology. An organoid is a miniaturized and simplified version of an organ produced in three-dimensional (3-D) culture that shows realistic micro-architecture and morphogenesis. It is derived from one or a few cells from tissues, embryonic stem cells, or induced pluripotent stem cells, which can self-organize in 3-D culture owing to their self-renewal and multiple differentiation capacity. Historically, attempts to create organs *in vitro* began with dissociation-reaggregation experiments. One of the elegant scientific findings by Townes and Holtfreter (1955) is that reaggregated cells become spatially segregated, and the final position of the reaggregated cells reflects their embryonic position by using dissociated cells from different germ layers of a neurula-stage embryo, suggesting changes in the selective tissue affinities during development. With the emergence of stem cell biology, the potential of stem cells to form organs was realized, indicating that the differentiated cells can organize into different structures resembling those found in multiple tissue types. The recent advent of organoid biology started with a shift from 3-D culture, allowing us to better understand brain development and function, together with providing novel models of human brain diseases, high-throughput screening of drug discovery platforms, and supply of surrogate sources of transplantation, as briefly discussed in this review article.

Sa et al. (2022) discussed a new research avenue for non-neuronal glial cells, particularly astrocytes in the hypothalamus. The hypothalamus is responsible for coordinating many physiological processes and behaviors, together with neuroendocrine functions, by linking the nervous and endocrine systems via the pituitary gland. The authors recently found that resident astrocytes in the hypothalamus dramatically transformed into reactive states even after three days of high-fat diet feeding. Under pathological conditions, such as high-fat diet-induced obesity, these reactive astrocytes induce the tonic release of GABA, one of the major inhibitory transmitters that may signal neighbor neurons, leading to the homeostatic integration of food intake and energy expenditure, as comprehensively discussed in this review article.

Hong and Nam (2022) thoroughly discussed the neuron-on-a-chip technology developed to study neurodevelopmental processes, such as neurite outgrowth, axon guidance,

Received 21 December, 2021; accepted 23 December, 2021; published online 28 February, 2022

eISSN: 0219-1032

synaptogenesis, and neuronal network dynamics. This review article systematically describes two core technologies: soft-lithography and microelectrode arrays. Soft lithography technology enables the fabrication of neural cell patterning and microfluidic channel devices to control nerve cell behaviors at a single-cell level via chemical and physical cues. A microelectrode chip array, which provides functional readout by measuring the electrophysiological signals from individual neurons, analyzes the functional connectivity of neuronal networks. These neurotools have become popular as a platform technology to investigate spatiotemporal information processing in neuronal networks.

Rah and Choi (2022) comprehensively discussed the strengths and limitations of a variety of microscopic tools to elucidate the microcircuits of the brain in terms of anatomical and functional connectivity among neurons. Although electron microscopy is the gold standard method for microcircuit reconstruction, its incompatibility with functional and molecular analysis limits its applications in connectome studies in neurobiology. The authors describe recent advances in various fluorescence microscopy techniques that offer a new possibility for reliable synapse detection in a large volume of neural circuits. The authors further discuss their recent study to analyze the long-range connectivity among the cortical region and the subcellular distribution of synapses in relatively large volumes of cortical tissue using super-resolution microscopy, which combines structured illumination microscopy (SIM) and array tomography to overcome the limitations of the SIM.

The last review article by Park et al. (2022) deals with their recent findings on neural circuits and molecular markers that correlate with behaviors related to animal survival, such as evasion, approach, and predation. The authors dissected and manipulated these innate behaviors using optogenetic stimulation, in part, together with fiber photometry and endoscopic calcium imaging tools. Upon perceived threat or danger that is accurately gauged, animals engage in ethologically relevant behavioral outputs. Interestingly, this review demonstrated that diverse neural circuits involved in three different behaviors appear to converge at the periaqueductal grey (PAG) regions, which may manage to integrate diverse neural information using modern neurobiology techniques.

Lastly, I would like to briefly mention the global trends and vision of advancement in novel neurotools in the next several decades. The US-funded BRAIN (Brain Research through Advancing Innovative Neurotechnologies) initiative was launched in 2013 and successfully passed its halfway point. This mega-funding initiative contributed to the development and implementation of a variety of innovative tools in an integrated manner to make fundamental new discoveries in neurobiology, eventually leading to the achievement of human whole-brain mapping or functional connectome. The second phase of BRAIN initiative (BRAIN2.0) will bring to the big picture by the organization of new discoveries from multi-approaches at multi-scales. We can predict a substantial acceleration of our understanding of the nervous system that will develop new therapeutic interventions to treat neural diseases over the next several decades. We also expect this scientific achievement to influence socioeconomic ramifications, including education, economics, ethics, and society in the future.

In this sense, it is important to note that the society for neuroscience in the U.S. suggests the future vision of neurobiology in the next several decades (Altimus et al., 2020). For instance, the highest resolution of whole-brain imaging at the structural and functional levels would be accomplished in the next two or three decades. Non-invasive ultrasonic imaging and neuroorganoid therapy are future-oriented medical interventions. Interestingly, within the next four decades, NeuroEngineering, including brain-machine interface (BMI) technology (Martino et al., 2020), will dramatically develop to gain access to artificial limb fluidity through neural activity to restore the perception of visual images for the blind person and to revitalize memory stored in discrete brain regions (Altimus et al., 2020). Along with such global trends and future vision, it would be quite pivotal for the Korean neuroscience community to re-attempt a grand challenge, such as the Korea Brain Initiative (Jeong et al., 2016) or its modified version in the near future.

ACKNOWLEDGMENTS

This work was supported by the NRF grant (NRF-2021R1A2C1004803) and DGIST start-up fund program of the Ministry of Science and ICT (2020010055) of Korean government awarded to K.K.

CONFLICT OF INTEREST

The author has no potential conflicts of interest to disclose.

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