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Author(s):
Fiscella, Michele; Ronchi, Silvia; Prack, Gustavo; Hierlemann, Andreas (iD)

FUNCTIONAL CHARACTERIZATION OF AXONS IN HUMAN IPSC-DERIVED NEURONS MODELING BRAIN DISEASES BY HIGH-DENSITY MICROELECTRODE ARRAYS

Michele Fiscella[1,2,*], Silvia Ronchi[1], Gustavo Prack[1] and Andreas Hierlemann[1]

1.Department of Biosystems Science and Engineering, ETH Zürich, Basel, Switzerland

2.MaxWell Biosystems AG, Zürich, Switzerland

* michele.fiscella@bsse.ethz.ch, michele.fiscella@mxwbio.com

Abstract

Axons play a central role in neuronal pathophysiologies of Parkinson's Disease (PD) and Amyotrophic Lateral Sclerosis (ALS). Human neurons with functional axons that can be used to model brain diseases can be generated in vitro by induced-pluripotent-stem-cell (iPSC) technology. High-Density Microelectrode Arrays (HD-MEAs) enable label-free and long-term recording of the electrical activity of axons. In this study, we compared the action-potential-propagation velocity along axons between human control neuron lines and isogenic neuron lines that have been genetically modified to model PD and ALS. Our findings indicate that axonal action-potential-propagation velocity can be used as an indicator for (1) electrophysiological phenotype characterization of multiple human iPSC-derived neuronal lines and for (2) testing the effects of drugs on axon physiology. We have used HD-MEA technology featuring 26'400 electrodes at 17.5 um pitch (MaxWell Biosystems AG). Commercially available human dopaminergic and motor neuron lines were plated on HD-MEA chips: (1) iCell® DopaNeurons, (2) MyCell® DopaNeurons α-synuclein (A53T) modeling PD, (3) iCell® Motor Neurons and, MyCell® Motor Neurons TDP43 (Q331K) modeling ALS, (Fujifilm Cellular Dynamics International). All neuronal lines were co-cultured with human astrocytes iCell® Astrocytes (Fujifilm Cellular Dynamics International). Each HD-MEA chips was plated with 100'000 neurons and 20'000 astrocytes. Axonal action potential velocities were compared across neuronal cultures by customer-written software in MATLAB. We found that control dopaminergic neurons and control motor neurons had significantly different axonal action potential velocities at DIV 28. Dopaminergic neurons featured average velocities of 500 mm/s, whereas motor neurons featured average velocities of 600 mm/s. Furthermore, we found that PD dopaminergic neurons showed a decrease of 15% in average velocity as compared to the control dopaminergic neurons. Finally, we found that ALS motor neurons showed an increase of 10% in velocity as compared to the control motor neurons. HD-MEA systems enable to access novel electrophysiological parameters of iPSC-derived neurons, which can be potentially used as biomarkers for functional phenotype studies and drug screening.

Funding Source