Exploring the role of neurodevelopmental disordersassociated proteins using brain organoids

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Genomic studies in large cohorts of patients affected by neurodevelopmental disorders have identified mutations in genes expressed at the synapses. Many of these genes have been extensively studied in adult animal models due to their role in regulating synaptic connectivity and transmission in matute neurons. However, most of the neurodevelopmental disorders-associated genes are expressed much earlier in the brain, at the stage of embryonic development when neurons are still immature and neurogeneis is prominent. The lack of experimental models hindered the capability of researchers to study the effects of gene mutations on human brain development. The advent of human pluripotent stem cells (hPSC) and hPSC-derived neuron and brain organoids allowed researchers for a much deeper investigation of the cellular and molecular mechanisms disrupted by mutations in neurodevelopmental disorders-associated genes during brain development. We studied the effect of deletions in SHANK3, a synaptic scaffolding gene found mutated in Phelan-McDermid Syndrome (PMS) patients. Using hPSC-derived neurons, we found that SHANK3 deletions affect excitatory synaptic transmission, synaptic connectivity and spines development in excitatory neurons. Recently, using hPSC-derived telencephalic organoids harboring SHANK3 deletions, we confirmed synaptic deficitis observed in neurons and we found dysregulation in the expression of clustered protocadherins. Our novel finding may provide new insights into the connectivity and developmental deficits associated with SHANK3 hemizygosity.

Biography

Dr. Chiola has completed his PhD at the age of 28 years from University of Turin in Italy. He is a postdoctoral reserach associate at the University of Utah School of Medicine in the Shcheglovitov Lab. He studies neuropsychiatric disorders and collaborates in many projects in the Lab and with external collaborators. He has published more than 3 papers as a first author in reputed journals and has been serving as an scientific board member of international foudations established by families of children affected by neurodevelopmental disorders.

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