P53 - iPSC-DERIVED 3D BRAIN ORGANOIDS CULTURED IN A BIOREACTOR AS AN IN VITRO MODEL FOR THE STUDY OF MICROCEPHALY IN AICARDI GOUTIÈRES SYNDROME

Rosalba Monica Ferraro [1] - Michele Manganelli [1] - Elena Laura Mazzoldi [1] - Marta Parigi [1] - Giovanna Piovani [2] - Jessica Galli [3] - Marco Cattalini [4] - Elisa Fazzi [3] - Silvia Giliani [1]

University of Brescia, "Angelo Nocivelli" Institute for Molecular Medicine, Department of Molecular and Translational Medicine, ASST Spedali Civili di Brescia, Brescia, Italia [1]
University of Brescia, Department of Molecular and Translational Medicine, Division of Biology and Genetics, Brescia, Italia [2]
University of Brescia, Department of Clinical and Experimental Sciences, ASST Spedali Civili di Brescia, Unit of Child Neurology and Psychiatry, Brescia, Italia [3]
University of Brescia, Dept. of Clinical and Experimental Sciences, ASST Spedali Civili di Brescia, Pediatric Clinic, Brescia, Italia [4]

The capability to reprogram patient-derived somatic cells to induce Pluripotent Stem Cells (iPSCs) and direct their differentiation towards Neural Stem Cells (NSCs) has provided a renewable source of expandable patient-specific cells to generate a valuable platform for *in vitro* disease modelling. The 2D monolayer cell culture has disadvantages, including the lack of heterogeneous cell-cell and “biomimetic” interactions, which can be partially overcome by the introduction of a 3D organoid culture. The iPSCs potential, combined with the modern 3D culturing technologies, may enable to exploit human brain-like tissues named “brain organoids”. Neurological genetic disorders can benefit the most from 3D modeling for its capability to generate an organized neuronal and glial network, otherwise only available from post-mortem samples. We deepened the *in vitro* 2D neuronal differentiation, generating and characterizing NSCs and neurons from iPSCs of 3 patients with Aicardi-Goutières syndrome (AGS), mutated in different genes: RNaseH2B, IFIH1 and TREX1. AGS is a severe neuro-inflammatory disorder with onset in early infancy. AGS patients exhibit microcephaly with demyelination and calcification. To date, mutations in 9 genes are responsible of the disease. As one of the features of AGS is the profound microcephaly, we generated and characterized 3D dynamic brain organoids culture in a bioreactor (Cel Vivo, ClinoStar system) from control and AGS iPSCs as a better *in vitro* model to explore the cytoarchitectural alteration typical of the disease. In particular, since to date the description of AGS iPSCs-derived brain organoids is documented only for TREX1 mutated-samples, we expanded the study cohort to investigate the pathogenetic contributions and interaction between neurons and glia also in other AGS-derived brain organoids characterized by specific genetic mutations.