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OC.11- 3D HUMAN MODELS TO UNDERSTAND THE NEUROGENIC ROLE OF CYSTATIN B IN HUMAN EPILEPSY EPM1

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EPM1 is an autosomal recessive neurodegenerative disorder that has the highest incidence among the progressive myoclonic epilepsies worldwide, characterized by stimulus-sensitive myoclonus and tonic-clonic epileptic seizures. Loss of function mutations in the gene encoding CYSTATIN B (CSTB) are the primary genetic cause of EPM1. CSTB is a small ubiquitous protein, identified as inhibitor of cathepsin family proteases. It is generally accepted that the loss of the antiprotease function of CSTB is the cause of EPM1 but the evidence supporting the involvement of CathepsinB is debatable. Here we model EPM1 and the role of CSTB by using patient-derived cerebral organoids, a 3D model of human brain development. To this aim, we collected blood samples from two patients with EPM1: one patient homozygous for the most common EPM1 mutation, a dodecamer amplification in the promoter of CSTB gene; and one young patient, heterozygous compound with promoter amplification and point mutation in intron 1. Starting from these 2 samples, we generated induced pluripotent stem cells (hIPSCs) that were then used to generate cerebral organoids. We found that EPM1-derived cerebral organoids show premature differentiation and alteration of progenitors proliferation related to controls. Moreover, we generated neurons derived from EPM1 and control cerebral organoids, confirming the results obtained in 3D cultures. Furthermore, the effects on progenitors proliferation are in line with previous results showed both in human cerebral organoids and in mouse brain, where CSTB or one of the pathological mutants were overexpressed, suggesting a role of CSTB in regulating early steps of human neurogenesis and development.