Defective Autophagy Disturbs Neural Migration and Network Activity in hiPSC-Derived Cockayne Syndrome B Disease Models

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Abstract : It is widely acknowledged that animal models do not always represent human disease. Especially human brain development is difficult to model in animals due to a variety of structural and functional species-specificities. This causes significant discrepancies between predicted and apparent drug efficacies in clinical trials and their subsequent failure. Emerging alternatives based on 3D in vitro approaches, such as human brain spheres or organoids, may in the future reduce and ultimately replace animal models. Here, we present a human induced pluripotent stem cell (hiPSC)-based 3D neural in a vitro disease model for the Cockayne Syndrome B (CSB). CSB is a rare hereditary disease and is accompanied by severe neurologic defects, such as microcephaly, ataxia and intellectual disability, with currently no treatment options. Therefore, the aim of this study is to investigate the molecular and cellular defects found in neural hiPSC-derived CSB models. Understanding the underlying pathology of CSB enables the development of treatment options. The two CSB models used in this study comprise a patient-derived hiPSC line and its isogenic control as well as a CSB-deficient cell line based on a healthy hiPSC line (IMR90-4) background thereby excluding genetic background-related effects. Neurally induced and differentiated brain sphere cultures were characterized via RNA Sequencing, western blot (WB), immunocytochemistry (ICC) and multielectrode arrays (MEAs). CSB-deficiency leads to an altered gene expression of markers for autophagy, focal adhesion and neural network formation. Cell migration was significantly reduced and electrical activity was significantly increased in the disease cell lines. These data hint that the cellular pathologies is possibly underlying CSB. By induction of autophagy, the migration phenotype could be partially rescued, suggesting a crucial role of disturbed autophagy in defective neural migration of the disease lines. Altered autophagy may also lead to inefficient mitophagy. Accordingly, disease cell lines were shown to have a lower mitochondrial base activity and a higher susceptibility to mitochondrial stress induced by rotenone. Since mitochondria play an important role in neurotransmitter cycling, we suggest that defective mitochondria may lead to altered electrical activity in the disease cell lines. Failure to clear the defective mitochondria by mitophagy and thus missing initiation cues for new mitochondrial production could potentiate this problem. With our data, we aim at establishing a disease adverse outcome pathway (AOP), thereby adding to the in-depth understanding of this multi-faced disorder and subsequently contributing to alternative drug development.

Keywords : autophagy, disease modeling, in vitro, pluripotent stem cells

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