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Manifestation of Huntington's disease pathology in human induced pluripotent stem cell-derived neurons

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Abstract

© 2016 Nekrasov et al.Background: Huntington's disease (HD) is an incurable hereditary neurodegenerative disorder, which manifests itself as a loss of GABAergic medium spiny (GABA MS) neurons in the striatum and caused by an expansion of the CAG repeat in exon 1 of the huntingtin gene. There is no cure for HD, existing pharmaceutical can only relieve its symptoms. Results: Here, induced pluripotent stem cells were established from patients with low CAG repeat expansion in the huntingtin gene, and were then efficiently differentiated into GABA MS-like neurons (GMSLNs) under defined culture conditions. The generated HD GMSLNs recapitulated disease pathology in vitro, as evidenced by mutant huntingtin protein aggregation, increased number of lysosomes/autophagosomes, nuclear indentations, and enhanced neuronal death during cell aging. Moreover, store-operated channel (SOC) currents were detected in the differentiated neurons, and enhanced calcium entry was reproducibly demonstrated in all HD GMSLNs genotypes. Additionally, the quinazoline derivative, EVP4593, reduced the number of lysosomes/autophagosomes and SOC currents in HD GMSLNs and exerted neuroprotective effects during cell aging. Conclusions: Our data is the first to demonstrate the direct link of nuclear morphology and SOC calcium deregulation to mutant huntingtin protein expression in iPSCs-derived neurons with disease-mimetic hallmarks, providing a valuable tool for identification of candidate anti-HD drugs. Our experiments demonstrated that EVP4593 may be a promising anti-HD drug.

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Keywords

Aging, Differentiation, GABAergic medium spiny neurons, Human induced pluripotent stem cells, Huntington's disease, Neurodegeneration, Neuroprotection, Nuclear indentations, Store-operated calcium entry