Modeling and correcting Huntington’s disease-associated myelin deficiency in human glial chimeras

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Country

Denmark

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Modeling and correcting Huntington’s disease-associated myelin deficiency in human glial chimeras

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3

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Research Abstract

HD is characterized by neuronal degeneration but is also associated with myelin loss, potentially reflecting dysfunction of myelin-producing oligodendrocytes. We have generated oligodendrocyte progenitor cells (OPCs) from human embryonic stem cells, derived from either huntingtin (mHTT)-mutant embryos or controls, and performed RNA sequence analysis. We identified a set of key transcription factors associated with oligodendroglial differentiation and

myelin biosynthesis to be significantly down-regulated in mHTT OPCs. These included MYRF, a transcription factor that coordinately activates myelin genes, which were concurrently down-regulated. We hypothesize that the hypomyelination of HD patients results from mHTT-dependent dysregulation of MYRF. We will test this hypothesis in a novel model of human glial chimeric mice, in which differentiation and myelinogenesis by OPCs may be observed and manipulated in vivo. Paired with TALEN-mediated forced expression of MYRF in HD OPCs, these experiments should provide sufficient molecular insight into the HD-dependent suppression of oligodendrocyte maturation as to potentially reverse it, thereby restoring myelinogenic competence. To that end, we will ask the following:

Further information available at:

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