Huntingtons disease: a novel developmental oligodendrogliopathy

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USA

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Huntingtons disease: a novel developmental oligodendrogliopathy

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5

The project/programme is most relevant to:

Huntington's disease

Keywords

Huntington Disease, Oligodendroglia, Huntington gene, white matter, Prosencephalon

Research Abstract

? DESCRIPTION (provided by applicant): Huntington’s disease: a novel developmental oligodendrogliopathy Huntington’s disease (HD) is a relentlessly progressive neurodegenerative

disorder that typically presents with progressive cognitive/motor deficits. Although HD exhibits a unitary genetic basis (mutant huntingtin [mHtt]), our understanding of HD pathogenesis remains poorly defined. The hallmark of HD is degeneration of striatal medium spiny neurons (MSNs). Therefore, study of HD has focused predominantly on cell autonomous mechanisms mediating MSN death. However, there is increasing recognition that HD pathology also encompasses dysfunction of oligodendrocytes (OLs), myelin and white matter tracts (WMTs). These defects occur during prodromal phases of HD, suggesting that non-cell autonomous mechanisms mediated by OLs may play important roles in HD pathogenesis. Here, we test the hypothesis that postnatal WMT abnormalities are: (1) secondary to defects in the second wave of developmental forebrain oligodendrogliogenesis leading to ectopic persistence of non-myelinating OLs from the first wave, and (2) necessary for region-specific profiles of forebrain vulnerability to neurodegeneration. This developmental hypothesis is based on our experimental data showing: (1) impairments in multiple NSC-mediated MSN developmental parameters in a HD knock-in mouse model, (2) early and stable OL impairments in HD mouse models/human pathological specimens, (3) key conjoint roles of Gsx2 in mediating MSN and OL second wave developmental functions, and (4) selective temporal ablation of mHtt after neural development recapitulates characteristic features of HD (EUREKA R01). Our Specific Aims are to define: (1) roles of ventrally- vs. dorsally-derived developmental OLs in HD WMT abnormalities, (2) pathogenic roles of OLs and WMT abnormalities in HD pathogenesis and therapeutic benefits of OL-based molecular genetic and cell replacement interventions. Our research approach will study: (I) differential ontogenic expression of Gsx2 in HD, (II) dynamic OL-specific lineage aberrations in HD, (III) molecular genetic rescue of Gsx2-dependent OL deficits in HD, (IV) role of HD-associated OL abnormalities in HD pathogenesis via conditional ablation of mHtt in OL precursors, (V) effects on HD onset/progression of OL cell replacement strategies. The Significance includes: (A) defining the developmental nature of HD OL lineage abnormalities, (B) establishing that a non-neuronal/non-cell autonomous mechanism is part of the pathogenic cascade leading to neuronal cell death, (C) establishing that HD represents a new class of primary developmental oligodendrogliopathy, (D) initiating entirely new directions for gene and cell based therapeutic studies during the prodromal phase based upon the HD-mediated OL developmental dysfunction. The Innovation is (1) proposing a novel mechanism underlying HD pathogenesis by incorporating a “”two-hit”” model including developmental forebrain OL deficits, (2) employing OL lineage-tracing to study the HD developmental oligodendrogliopathy, (3) using time-specific conditional genetic manipulations to rescue the putative HD developmental oligodendrogliopathy, (4) using cell replacement of OL developmental species to treat HD.

Lay Summary

PUBLIC HEALTH RELEVANCE: The mechanisms that lead to selective neuronal cell death in neurodegenerative diseases (e.g., Huntington’s disease [HD], Alzheimer’s disease and Parkinson’s disease) remain largely unknown, and no effective disease modifying therapies exist. HD represents the archetypal genetically determined adult onset neurodegenerative disease, and advances in HD research may provide important insights regarding these other pernicious and difficult to treat chronic progressive neurological disorders. The proposed studies focus on the novel idea that the mutant gene responsible for causing HD promotes neuronal cell death indirectly by impairing the development and function of one important class of neural support cells (i.e., oligodendrocytes).

Further information available at:

Types:

Investments > €500k

Member States:
United States of America

Diseases:
Huntington's disease

Years:
2016

Database Categories:
N/A

Database Tags:
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