Huntington’s Disease

What is Huntington’s?
• Neurodegenerative disease
• Characterized by aggregates of misfolded proteins
• If gene is inherited the disease is acquired
• Can be detected through blood test
• NO KNOWN CURE

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A Molecular Look into the Hunt
Pathway in Huntington’s Disease

Huntington’s Neuron v. Normal Neuron

Coronal brain section. Severe striatal atrophy in Huntington’s patient (left) and control (right)

Huntington Protein

CAG nucleotide sequence

AKA: Polyglutamine tract
Location: Chromosome 4
Codes for: Glutamine

Mutant Huntingtin
Function: Not clearly known
Normal Htt: <36 repeats CAG
Mutant Htt: >36 repeats CAG

• More repeats of CAG, the more severe pathology
• mHtt forms aggregates

Onset v. Repeats

Symptoms

Correlation between the number of CAG repeats and age of onset

Phase of signs and symptoms as disease progresses

Huntington Protein

CAG Repeats
Death
Age

What research is being done for Huntington’s Disease?
• Why are cells dying specifically in the striatum?
• Are neural transplants a viable form of treatment?
• What molecular pathways are there to degrade protein aggregates?
• Can gene mutations help with possible therapies for HD?

The Hunt for Knowledge

Treatment for Chorea Symptoms

Tetrabenazine
Neuroleptics
Benzodiazepines

Treatment for Psychiatric Symptoms

Post Synaptic Membrane
Protopic Membrane
Selective Serotonin Reuptake Inhibitors

References


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Medical Mysteries of HD

Hunting for Striatal Cells

Why is there cell death in the striatum?

Rhes, a Striatal Specific Protein, Mediates Mutant-Huntingtin Cytotoxicity.

To target a pathway to degrade mutant huntingtin and increase cell survival.

FINDINGS

1. Rhes binds to mutant huntingtin and decreases aggregation of mHtt
2. Rhes acts as an E3 ubiquitin ligase
3. Cysteine is required for Rhes function


Hunting for Mutants

Can adding mutations on serine 13 and 16 in transgenic mice lead to a possible therapy for Huntington’s Disease?

A phosphomimetic (SD) mutation or a phosphoreistant (SA) mutation will help relieve motor and behavioral deficits, aggregation, and neurodegeneration.

FINDINGS

1. Mice with the SD mutation live and are healthy, mice with the SA mutation die.
2. Mice with any of the SA mutation usually died in vitro, all died from HD eventually. Those mice with the SD mutation were healthy.


Hunting for a Treatment

Can dying neurons be replaced as a viable treatment?

To replace dying cells as a viable treatment.

FINDINGS

1. Grafts do not survive long term
2. Grafted neurons die faster than patient’s neurons
3. Death of projection neurons
4. Inflammatory response targets grafts


Hunting for a Target

How can mutant huntingtin protein be degraded?

To target a pathway to degrade mutant huntingtin and increase cell survival.

FINDINGS

1. The lysine of mutant huntingtin is acetylated by HAT and deacetylated by HDAC.
2. Inhibition of HDAC and an increase in HAT leads to the degradation of mHtt and an increase in cell survival.
3. Mutations on lysine may prevent acetylation and lead to an increase in cell death.