Huntington's Disease: Pathophysiology and Clinical Prospects

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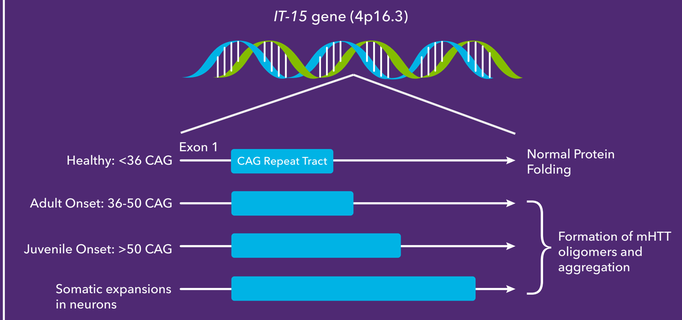
Huntington's disease (HD) is a severe monogenic neurodegenerative disorder. It is caused by a dominantly inherited CAG trinucleotide repeat expansion in the huntingtin (HTT) gene, which encodes for an elongated glutamine stretch in the HTT protein. The progressive brain degeneration in HD is characterized by the prevalent loss of GABAergic medium spiny neurons (MSN) in the striatum[1]. Clinical features include progressive motor dysfunctions and cognitive impairments[2].

Genetic and Clinical Manifestations

The monogenetic defect responsible for HD is a CAG trinucleotide repeat expansion in exon 1 of the IT15/HTT gene on chromosome 4, encoding an expanded polyglutamine (PolyQ) repeat in the huntingtin protein, which forms mutant HTT (mHTT). Individuals with less than 36 CAG repeats remain unaffected, however the presence of more than 40 CAG repeats consistently causes disease within a normal lifespan[3]. The number of CAG repeats inversely correlates with the age of disease onset as well as progression of motor and cognitive deficits. Clinical features typically manifest around the fourth decade. The most common motor behavior symptom of HD is chorea, which is characterized by unwanted rapid and short-lasting movements in the limbs, face, and trunk. In addition, patients exhibit severe cognitive and psychological symptoms which worsen with time[2].



Focus on DNA Repair

Following inheritance of an expanded CAG repeat, a process of repeat expansion continues in somatic cells throughout life; higher repeat expansion rates correlate with earlier age of onset and more severe disease progression[4]. Genome-wide association studies (GWAS) have identified genes involved in DNA damage and mismatch repair pathways as genetic modifiers of disease progression and are now directly implicated in the CAG repeat expansion process[5]. This provides an exciting opportunity for HD treatment, as drugs that target identified DNA repair mechanisms have the potential to slow or even reverse somatic CAG expansion, thereby providing a therapeutic delay to disease onset[5,6].

HTT Functions

The HTT protein has several functions within the cell. HTT interacts with various organelles and is involved in mediating:

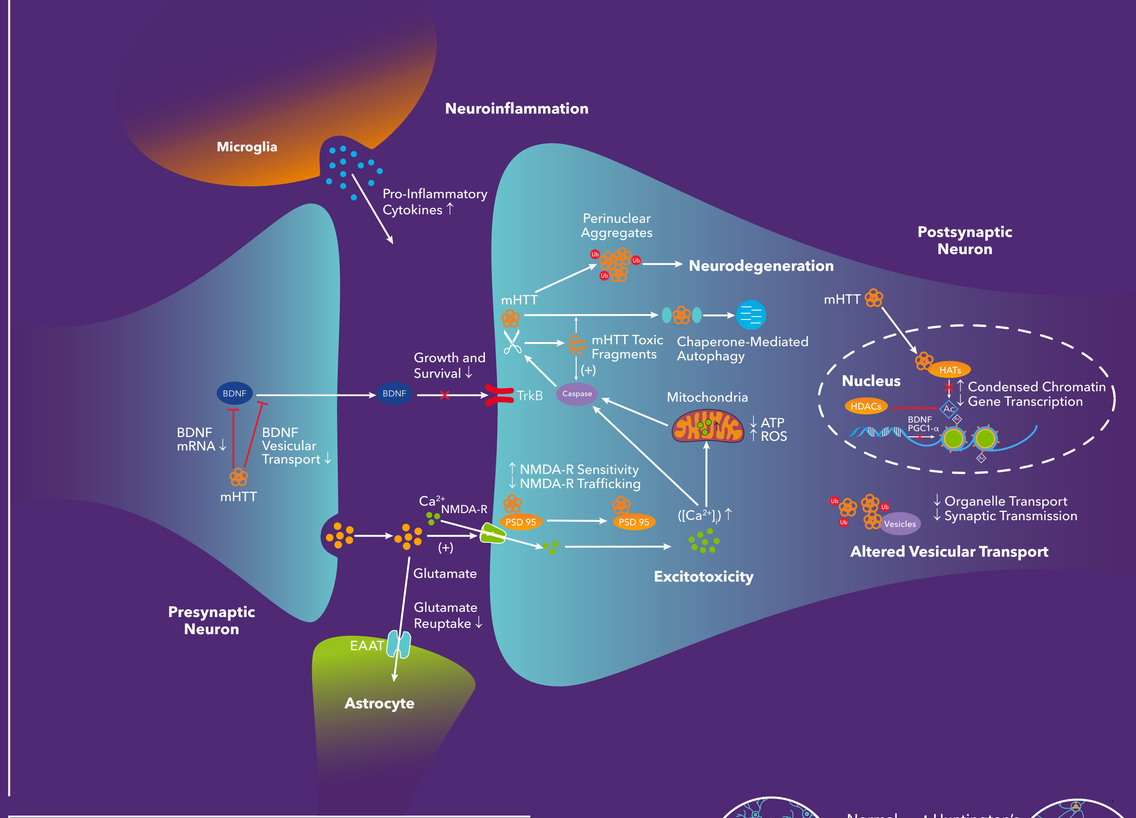
- Chromatin remodeling and gene transcription[7,8]
- Neuroprotection (BDNF transcription and trafficking)[9,10]
- Cell survival (HTT is anti-apoptotic)[7]
- Calcium homeostasis[11]
- Mitochondrial function and trafficking[10]
- Intracellular trafficking and synaptic vesicle recycling[7,8]

The reduction of HTT and coexistence of mHTT results in the disruption of these cellular processes, culminating in cell death[8].

Therapeutic Strategies

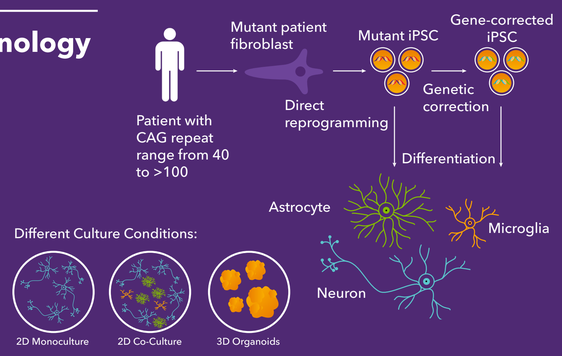
Currently, there are no treatment options for HD that can halt or reverse the disease. Commonly used symptomatic treatments attempt to improve the quality of life of affected patients by addressing the movement, cognitive and psychiatric symptoms. Novel therapeutics with the intent of slowing disease progression are being developed. These approaches target pathways specific to HD biology. Among these approaches, mHTT protein lowering therapies hold great promise[12].

Molecular Events in Neurons



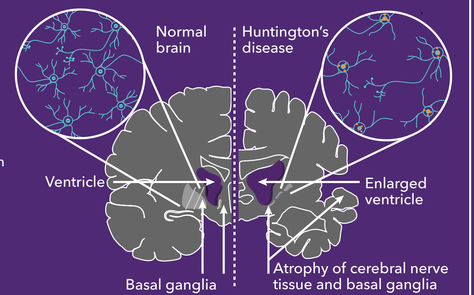
HD Modeling with iPSC Technology

Somatic cells can be reprogrammed to a pluripotent state by the exogenous introduction of pluripotency associated transcription factors such as OCT4, KLF4, SOX2 and c-MYC[13]. The generated human induced pluripotent stem cells (iPSCs) can differentiate into cells of all germ layers, including brain cells like neurons, astrocytes and microglia. iPSCs can be derived from HD patients in order to retain the patient's genetic background and are accessible for gene editing, e.g. to correct the mHTT to produce isogenic control cells[14]. Nowadays, iPSC-derived cells can be studied in different culture conditions, ranging from 2D monocultures to 3D brain-like organoids[15].



Huntington's Disease Brain Pathology

The left hemisphere shows a normal healthy brain, while the right hemisphere shows HD-specific histopathological hallmarks. The most striking feature of HD is neuronal loss in the striatum along with enlarged lateral ventricles. In progressed stages of the disease, degeneration also occurs in the cerebral cortex[16]. At a molecular level the mHTT protein forms intracellular aggregates in neurons of affected brain regions that appear as inclusion bodies[17]. Expanding polyglutamine length in the mHTT protein induces increased generation of toxic mHTT oligomers and presence of cellular inclusion bodies.



References

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Tocris Products

Trk Receptors
ANA 12
BDNF (human)
7,8-Dihydroxyflavone
LM 22A4

NMDA Receptors
D-AP5
DL-AP5
(R)-CPP
(RS)-CPP
Ibotenic acid
Memantine (+)-MK 801

Kainate Receptors
CNQX
DNQX
Kainic acid
Topiramate

Glutamate Transporters
Dihydrokainic acid
DL-TBOA
LDN 212320
TFB-TBOA

Glutamate (Metabotropic) Receptors
CDPPB
CHPG Sodium salt
(RS)-3,5-DHPG
(S)-3,5-DHPG
L-Quisqualic acid
LY 379268
(S)-MCPG
MPEP
MTEP
VU 0360172

Heat Shock Proteins
17-AAG
Geldanamycin
VER 155008

Stem Cell Differentiation
DAPT
DMH-1
Dorsomorphin
Fluoxetine
Forskolin
IBMX
Purmorphamine
SAG
SB 431542
SU 5402

iPSCs
CHIR 99021
Valproic acid sodium salt

Histone Deacetylases
SAHA
Trichostatin A

SIRT
EX 527
Nicotinamide
Resveratrol

Histone Acetyltransferases
Anacardic acid
C 646

Caspases
Cisplatin
Z-DEVD-FMK
Z-VAD-FMK

Calpains
Acetyl-Calpastatin (184-210) (human)
Calpeptin
PD 150606

Cathepsin
CA 074
E 64
E 64d

IP_3 Receptors
2-APB
(-)-Xestospongin C

Mitochondrial Permeability Transition Pore
Cyclosporin A
TRO 19622

Proteasome
Lactacystin
MG 132

Autophagy
Bafilomycin A1
(±)-Bay K 8644
Dexamethasone
LY 294002
Rapamycin
Taxol
Thapsigargin
Torin 1
Tunicamycin

Dopamine Receptors
Dopamine
Olanzapine
Risperidone
SCH 23390
SKF 38393
Tetrabenazine

Adenosine A_{2A} Receptors
CGS 21680
Istradefylline
SCH 58261
ZM 241385

Neuroprotective Compounds
Minocycline
N-Acetylcysteine amide
Riluzole

Caged Compounds
MNI-caged-L-glutamate
RuBi-Glutamate
RuBi-GABA