Huntington’s Disease: Pathophysiology and Clinical Prospects

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Huntington’s disease (HD) is a monogenic neurodegenerative disorder with autosomal dominance. Progressive brain degeneration is characterized by the prevalent loss of GABAergic medium spiny neurons (MSN) in the striatum. Clinical features include progressive motor dysfunctions and cognitive impairments.1 HD is caused by an extended repeat in the Huntingtin (HTT) gene, which then encodes for an elongated glutamine stretch in the protein.2 Induced pluripotent cell (iPSC) technology has also been used for the pathological modeling of HD.3

Genetic and Clinical Manifestations

The genetic defect responsible for HD is a CAG triplet repeat expansion on exon 1 in the IT15 gene on chromosome 4, encoding an expanded polyglutamine (PolyQ) region of the protein Huntingtin (htt), which forms mutant htt (mHtt). The presence of more than 40 CAG repeats causes disease within normal lifespan, whereas longer repeats predict early disease onset. Therefore, the number of CAG repeats correlates directly with the phenotypic severity. As the preclinical stage of HD is defined by subtle changes in personality and cognitive ability without neuropathological features, diagnosis can only occur at a later stage when specific histopathological hallmarks and advanced symptoms are present. Early neuropathological hallmarks include striatalatrophy, while progressive stages show degeneration in the basal ganglia and the cerebral cortex.4

HD Modeling with iPSC Technology

Somatic cells can be epigenetically reprogrammed to a pluripotent state by the enforced expression of specific transcription factors. These so-called human induced pluripotent stem cells (hiPSCs) can then be differentiated into any cell type.5 Of specific transcription factors. These so-called human induced pluripotent stem cells (hiPSCs) can then be differentiated into any cell type. 5 Of specific transcription factors. These so-called human induced pluripotent stem cells (hiPSCs) can then be differentiated into any cell type. 5

Glia1

BDNF (brain-derived neurotrophic factor) is a neurotrophin important for neuroprotection in stratal neurons. It is synthesized in the cortex and transported to MSNs via the cortico-striatal tract. BDNF binds to TrkB receptors (TrkB), which activate multiple signaling cascades such as anti-apoptotic enzyme activation, glutamate receptor transcription and calcium binding protein expression. mHtt disrupts BDNF transcription and trafficking, resulting in neuronal vulnerability.6

HD Function

mHtt interacts with various organelles including the nucleus, endoplasmic reticulum and mitochondria, and is involved in mediating:
• Chromatin remodeling and gene transcription7
• Neuroprotection (BDNF transcription and trafficking)8
• Cell survival (mHtt is anti-apoptotic)
• Calcium homeostasis
• Mitochondrial function and trafficking8

Huntington’s Disease Pathways

Gene transcription with the transcriptional machinery and enzymes involved in chromatin remodeling to influence gene expression. Investigations based on microarray assays show a change in expression of a large number of genes, even before the onset of symptoms.9 mHtt represents the transcription of SP-1 dependent genes by interacting with SP-1, TFE3 and TFE3B. It also interacts with cAMP response-binding protein (CREB) and FHL resulting in a reduced transcription of these cellular processes, culminating in cell death.10

Neurodegeneration

mHtt disrupts BDNF transcription and trafficking, transcription and calcium binding protein expression. mHtt interacts with various organelles (including, the nucleus, endoplasmic reticulum and mitochondria), and is involved in mediating:
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mHtt and HD neuronal vulnerability can result from the disruption of these cellular processes, culminating in cell death.9

HD Pathways

mHtt is one of the major excitatory neurotransmitters in the central nervous system, acting via activation of metabotropic or kainate-like glutamate receptors. In HD, the NMDA glutamatergic receptor is over-stimulated due to hyperactivity of this ion channel. Therefore, an increased glutamate release is caused by excitotoxic and a decrease in glutamate uptake by glial cells. Persistent NMDA-R activation causes the production of Ca2+ influx, which further results in a chronic increase of intracellular Ca2+ via Ca2+-induced Ca2+-release (CICR). This results in caspase activation, impaired mitochondrial Ca2+ buffering, and thus neuronal toxicity. Enhanced NMDA-R function could also be a result of a decreased interaction with postsynaptic channel protein (PSD-95) (PSD95). The mHtt-HAP-1 complex may also contribute to Ca2+ excitotoxicity by enhancing IP3 receptor activity.10

Neurodegeneration

mHtt binds more tightly to vesicles, which reduces their mobility and results in reduced vesicle release by cortical afferents and a decrease in glutamate release.8 Fewer synaptic vesicles than normal axons and also fewer synaptic vesicles than normal axons and also fewer synaptic vesicles than normal axons and also fewer synaptic vesicles than normal axons and also fewer synaptic vesicles than normal axons and also fewer synaptic vesicles than normal axons and also fewer synaptic vesicles than normal axons and also fewer synaptic vesicles than normal axons and also fewer synaptic vesicles than normal axons and also fewer synaptic vesicles than normal axons and also fewer synaptic vesicles than normal axons and also fewer synaptic vesicles than normal axons and also fewer synaptic vesicles than normal axons.11

Neuroprotective (BDNF transcription and trafficking)

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HD neurons present abnormalities in neurotransmitter transmission. Astrocytes containing iHgtg aggregates have fewer synaptic vesicles than normal astrocytes and also present a reduction in glutamate release. Furthermore, HD neurons, which is involved in mitophagy, which reduces its association with HAP-1.11

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