CUSJ
COLUMBIA UNDERGRADUATE SCIENCE JOURNAL

Molecular Mechanisms and Clinical Features of Huntington Disease: A Fatal Neurodegenerative Disorder with Autosomal Dominant Inheritance

Neelabh Datta[1]

[1]Department of Biochemistry, Asutosh College (Affiliated to University of Calcutta), 92, Shyama Prasad Mukherjee Rd, Kolkata, West Bengal, 700025, INDIA

KEYWORDS: Huntington's disease, neurogenetics, molecular mechanisms, pathophysiology, therapy

ABSTRACT: Huntington disease (HD) is a fatal genetic disorder that affects the movement and cognition of affected individuals. It is inherited in an autosomal dominant manner, meaning that each child of a parent with HD has a 50% chance of inheriting the mutated gene. The mutation involves an expansion of a trinucleotide repeat (CAG) in the HD gene, which is located on the short arm of chromosome 4p16.3. The HD gene encodes a protein called huntingtin, which has an unknown function. The number of CAG repeats determines the severity and onset of the disease. Normal individuals have 26 or fewer repeats, while HD patients have 40 or more repeats. Individuals with 27 to 35 repeats do not develop HD, but they can pass on the mutation to their offspring, especially if the mutation is inherited from the father. Individuals with 36 to 39 repeats may or may not develop HD, depending on other factors. The more CAG repeats, the earlier the symptoms appear. HD is the most extensively studied neurodegenerative disorder with a genetic cause. There are genetic tests available to diagnose HD and to predict the risk of developing HD in asymptomatic individuals. There are also prenatal and preimplantation tests to prevent the transmission of HD to the next generation. HD is characterized by involuntary movements called chorea, which affect all muscles and impair all psychomotor functions. HD patients also suffer from cognitive decline and psychiatric symptoms, such as mood disorders and social changes. These symptoms are chronic and progressive, leading to complete dependence and death. Chorea can also be caused by other conditions, such as metabolic disorders or drug-induced side effects. Neuroimaging techniques, such as MR imaging, fluorodeoxyglucose positron emission tomography (FDG-PET), MR spectroscopy, and diffusion tensor imaging, can help to diagnose HD and monitor its progression. The pathophysiology of HD involves the loss of neurons and the dysfunction of neurotransmitter systems, especially the dopaminergic system. There is no cure for HD, but there are treatments to manage the symptoms and to improve the quality of life of HD patients. These include pharmacological interventions, such as dopamine receptor antagonists or depleters, and non-pharmacological interventions, such as psychological and social support. HD is a devastating disease that poses many challenges for patients, families, and healthcare providers. There is hope that gene-targeted therapies will be developed in the near future to stop or slow down the disease process.

INTRODUCTION

Huntington disease (HD) is a fatal neurodegenerative disorder that affects the CNS and causes motor, cognitive, and behavioural problems in the patients [1]. The disease is inherited in an autosomal dominant manner and is caused by a mutation in the Htt gene that results in an expansion of the polyQ domain of the Htt protein beyond 36 glutamines [3]. The brain cells of HD patients have misfolded polyQ Htt proteins that form

clumps, unlike the normal individuals who have diffuse localization of Htt [12]. The length of the polyQ expansion determines how fast the aggregation occurs [13]. The normal function of the cell to recycle and degrade proteins and produce energy is disrupted by the misfolded polyQ Htt, which also binds to other proteins such as CREB binding protein and depletes them from the cell [14]. This leads to a toxic effect of the mutant Htt, but it also affects the normal function of the wildtype Htt, which does not have the polyQ expansion [2, 15]. Therefore, any treatment for HD must consider both the gain-of-function and the loss-of-function effects of the mutant Htt. The age of onset of HD depends on the length of the polyQ expansion, with longer expansions causing earlier and more severe symptoms [4]. The polyQ length explains 60-70% of the variation in the age of onset, while the rest is influenced by environmental and genetic factors [5].

The main feature of HD pathology is the death of the GABAergic MSN in the striatum, which is a part of the brain that controls movement and cognition [2, 6]. The death of the MSN is accompanied by inflammation and activation of glial cells, which are the support cells of the CNS [2]. Microglia, which are the immune cells of the CNS, are activated in both early and late stages of HD and cause damage to the neurons in the striatum and cortex [7]. Astrocytes and oligodendroglia, which are the cells that provide nutrients and insulation to the neurons, are also increased in HD brains, especially in the globus pallidus and the white matter surrounding it [8]. HD patients also show a significant loss of brain volume in different regions, such as the cerebral cortex, the telencephalic white matter, the putamen, and the caudate nucleus [2, 9, 11]. The loss of brain volume can be detected even before the symptoms of HD appear, indicating an early degeneration of the brain [10]. HD is a disease that affects the whole brain and causes progressive deterioration of the patients' functions and quality of life. There is no cure for HD, and the current treatments are only palliative and symptomatic.

Structure of the Huntingtin Protein

The huntingtin (Htt) protein is a molecule that is found in humans and other vertebrates, and it has a very similar structure and function among them [2,16]. It is a big protein, with a molecular weight of about 350 kDa, and it has a shape that is long and flexible [17,18]. The protein is made up of many repeated units called HEAT (Huntingtin, Elongator factor3, PR65/A regulatory subunits of PP2A, and Tor1), which help the protein to interact with other proteins and to form complex structures [2,24]. One of the special features of the Htt protein is that it has a region near the beginning of the protein that contains many glutamine residues, which are amino acids that have a nitrogen atom in their side chain [2]. This region is called the polyQ tract, and it starts from the 18th amino acid in the protein [2]. The number of glutamines in the polyQ tract can vary a lot, and this can affect how the protein works and how easily it dissolves in water [27,30]. In most people, the polyQ tract has around 20 glutamines, but in some people, it can have more than 40 glutamines, and this can cause a brain disease called Huntington's disease (HD) [20,21,22]. The polyQ tract is surrounded by another region that has many proline residues, which are amino acids that have a ring-shaped side chain [31]. This region is called the polyP tract, and it helps the protein to stay dissolved in water and to interact with proteins that are involved in moving things inside the cell [31,32]. The polyQ tract is not present in all animals that have a similar protein to Htt, but it is very important for the brain functions of animals that have it,

as shown by experiments with mice that do not have the polyQ tract [2,29]. The polyQ tract can also form structures that look like zippers, and these structures can bind to other parts of the protein or to other proteins that have similar structures [2,28]. The Htt protein is therefore a very complex and versatile protein that is involved in many different processes in the cell. The way that HD is inherited and how it affects different people is related to the way that the polyQ tract can change in size and cause problems, which is caused by an increase of the number of repeats of three nucleic acids (C, A, and G) in the first exon of the HD gene, which is located on chromosome 4p16.32 [19].

Htt has various features that allow it to move between the nucleus and the cytoplasm of the cell [2]. It has a nuclear export signal (NES) at the end of its C-terminal domain, which enables it to exit the nucleus [33]. It also has a domain at the beginning of its N-terminal domain, which consists of 18 amino acids and interacts with TPR, a protein that is part of the nuclear pore complex and facilitates nuclear import [33]. This domain also forms a membrane-binding domain that has an amphipathic alpha helical structure and can reversibly bind to different types of vesicles, such as those derived from the endoplasmic reticulum (ER), endosomes, and autophagosomes [34]. This domain is essential for the normal function of Htt, as mutations or deletions in this region cause Htt to accumulate in the nucleus and induce cellular toxicity [33]. Htt is also subject to proteolytic cleavage by various enzymes, such as caspases and calpains, which are conserved among higher vertebrates [35]. These enzymes generate fragments of Htt that are found in the nucleus, but their role is unclear. The proteolysis of Htt is influenced by the cellular context, as it is increased in diseased brains and more selective for the fragments that have the N- and C-terminal domains, especially in the striatum [2,36]. Another enzyme that can produce N-terminal fragments of Htt is cathepsin, which belongs to the lysosomal degradation pathway [37]. Htt can also undergo different types of post-translational modifications in its N-terminal region, such as ubiquitination, sumoylation, and phosphorylation by kinases like Akt, ERK1, and Cdk5 [2,38]. The phosphorylation level of Htt is regulated by S/T phosphatases PP1 and PP2A [39]. Furthermore, Htt can be palmitoylated in its N-terminal region through the interaction with Huntingtin-Interacting Protein 14 (HIP 14) [40]. Palmitoylation is a mechanism that is used by several proteins that are involved in vesicle trafficking to maintain their proximity to the plasma membrane [2]. Htt is highly expressed in the human brain and testes [41]. In the brain, it is present in both neurons and glial cells [42]. Htt has a complex subcellular localization pattern, which may depend on its conformational state, as different antibodies that recognize different epitopes within the protein show different subcellular staining profiles [43]. Htt is not only localized in the nucleus, ER, and Golgi complex, but also in the axons and synapses of neurons [41], where it is associated with microtubules, caveolae, and synaptosomes [41].

Significance and Function of the Huntingtin Protein

The function and role of the huntingtin protein is still unclear, despite the fact that its genetic location was identified a long time ago. Some studies have proposed that huntingtin is involved in regulating gene expression and transporting molecules inside the cell, based on its presence in both the cytoplasm and the nucleus and its frequent interactions with other proteins [44]. The huntingtin protein also plays a role in neuronal development, synaptic transmission, axonal transport, and autophagy [51]. The huntingtin

gene has a segment of DNA that repeats the sequence CAG, which codes for the amino acid glutamine. In normal huntingtin proteins, this segment has less than 27 repeats, and people with 27 to 35 repeats (called transitional alleles) [45] do not develop the disease, but they may pass on longer repeats to their offspring. People with 36 or more repeats will develop the disease [46]. The number of CAG repeats tends to increase in each generation, which means that the disease becomes more severe and appears earlier in life. This phenomenon is called "anticipation" [47]. The age of onset of the disease is inversely related to the number of CAG repeats. Therefore, people with juvenile- and infantile-onset HD have more repeats than their parents and show symptoms earlier [48].

The huntingtin protein is expressed in many different types of cells, but it is especially abundant in the brain and the testes, and to a lesser extent, in the liver and the lungs [49]. It has a protective role against cell death, but when it is mutated or underexpressed, it causes early apoptosis and dysfunction. The mutation that causes HD is an expansion of the CAG repeats, which results in a longer stretch of glutamine in the protein [46]. This leads to the formation of abnormal aggregates of the protein in the nucleus and the cytoplasm of the cell, which disrupts the normal balance of the cell and triggers apoptosis [50]. The aggregates also interfere with the normal function of huntingtin and its interacting partners, leading to neuronal degeneration, inflammation, oxidative stress, mitochondrial dysfunction, and impaired autophagy[52]. The most affected brain region is the striatum, which is involved in motor control and cognition, followed by the cortex, which is responsible for higher cognitive functions [53]. The symptoms of HD include chorea, dystonia, rigidity, bradykinesia, cognitive impairment, and psychiatric disturbances [54]. There is no cure for HD, but some treatments can help to manage the symptoms and improve the quality of life of the patients [55].

Clinical Indicators of Huntington Disease

HD affects the different aspects of behaviour, cognition, and motor function of humans [51]. The disease has three subtypes, depending on the age of onset: adult-onset, juvenile-onset, and infantile-onset. The most common subtype is adult-onset HD, which usually manifests in the fourth or fifth decade of life. Patients with adult-onset HD experience a range of behavioural symptoms, such as irritability, agitation, loss of inhibition, and aggression, which often precede the motor symptoms [46,52]. The motor symptoms include involuntary movements (chorea), which become less prominent as the disease progresses and are replaced by rigidity and abnormal muscle contractions (dyskinesia). Patients also lose their ability to maintain a sustained voluntary muscle contraction and their fine and gross motor skills, leading to severe disability and dependence [46,52]. The cognitive symptoms include impairment of memory, executive function, language, and visuospatial skills, which worsen over time and result in dementia [51]. The disease course of adult-onset HD is typically 15–20 years from the onset of symptoms to death [51]. The other two subtypes, juvenile-onset and infantile-onset HD, are much rarer and account for about 10% of HD cases. They are characterized by an earlier onset of symptoms, usually before the age of 20, and a more rapid progression of the disease [46,53]. The main features of these subtypes are rigidity, dyskinesia, and cognitive decline, with little or no chorea [46,53]. These patients often show signs of motor deterioration and poor academic performance before they are diagnosed [46,53].

Genetic Modifiers of Huntington's disease

The discovery of the HD defect [54] prompted many researchers to investigate the role of HD genes that were chosen based on their functional relevance. However, a new approach emerged in the early 21st century, which was based on two major advances in human genetics: firstly, the identification of common genetic variations across the genome, known as single nucleotide polymorphisms (SNPs), and secondly, the development of oligonucleotide array technology, which enabled the simultaneous genotyping of hundreds of thousands to millions of SNPs for unbiased genetic studies [55]. This approach, called genome-wide association analysis (GWA), allowed the researchers to scan the entire genome for genetic factors that influence the HD phenotype, without relying on prior knowledge of gene function. To apply this approach to HD with sufficient statistical power, three additional requirements had to be met: firstly, the availability of genomic DNA from a large number of HD subjects for genotyping; secondly, the definition of a robust phenotype that accounted for the effects of the CAG repeat size, which is the main determinant of the HD phenotype; and thirdly, the exclusion of any potential modifier factors that are linked to HTT and act in cis to modify the effect of the mutation, as these factors would confound the genome-wide search [55].

Statistically assessing the relationship between the length of inherited CAG repeats and the age of motor onset provided a vigorous HD phenotype that accounted for the effect of CAG repeats. Due to the danger of including inexplicably influential outliers, the analysis was limited to CAG repeat lengths typical of adult-onset (40 to 53–55) and sufficient representation of subjects to guarantee consistent results [56]. Based on their inherited CAG repeat lengths, >90% of HD subjects met these criteria, allowing a standard curve to be produced that relates CAG repeat size to average age-at-onset. In the absence of the effects of the CAG repeat size, an evaluation of this expected age-at-onset with the individual's observed age-at-onset provided the phenotype for analysis of genetic effects on onset [57]. It was fundamentally a matter of subtracting the expected age-at-onset from the observed age-at-onset to obtain the test phenotype, or residual age-at-onset, which was either a positive or negative number of years based on whether the subject's onset was later or earlier than anticipated. It was possible to test whether genetic variations at the HTT locus other than the CAG repeat size affect age-at-onset by using residual age-at-onset as a relevant HD phenotype and several thousand unrelated HD subjects [55]. In order to examine this, common single nucleotide polymorphisms (SNPs) were compiled across the gene and defined as haplotypes (i.e. the linear array of alleles at multiple SNPs along the chromosome, conducted as a physically linked set to progeny—basically a digital fingerprint for the HTT region) [55]. In addition, expanded CAG alleles associated with HD were found in multiple haplotypes, indicating that multiple independent ancestral HD CAG expansion mutations contributed to the contemporary population of HD individuals [58]. The most common haplotypes, representing more than 83% of HD subjects, were not related with differences in onset age, which suggests that genetic factors usually act in transfer through genes detached from HTT [58]. Accordingly, HD is viewed as a prototypical autosomal dominant genetic disorder based on whether it is passed on to progeny (or not), but the timing of disease onset is actually polygenic, determined by the combination of CAG repeats and other genetic factors.

Factors that play a role in the development of HD

1. Mitochondrial disorder

In early studies, functional abnormalities in mitochondria were discovered, indicating that mitochondrial dysfunction plays an essential role in the pathogenesis of HD and this is usually seen in the early disease process. The caudate and to a lesser extent the cortex of post-mortem HD brains have succinate dehydrogenase deficiency, a component of both the Krebs cycle and the electron transport chain's complex II. As compared to levels in matched control brains, HD brains demonstrated a significant decrease in complex II activity in the caudate nucleus (roughly 50%) [67]. In addition to reductions in complex II activity, complex III activity in the caudate and putamen, as well as complex IV activity in the putamen, have decreased as well [67]. In spite of this, since most of these patients suffered from advanced neuropathy, including severe striatal atrophy (pathological grades 3 and 4 of HD), mutations in mitochondrial sources (i.e., glial, neuronal, etc.) may have occurred [59].

2. Oxidative stress due to ROS

Reactive oxygen species (ROS) are produced in excess in the body, which results in oxidative stress when the body is unable to detoxify them and repair the damage they cause. Animal models with HD showed increased levels of malondialdehyde, 8-hydroxydeoxyguanosine, 3-nitrotyrosine, and heme oxygenase oxidative damage products, and free radicals in the areas of degeneration in the brain of HD affected individuals which propose that oxidative stress is connected with the disease, either as a primary event or a secondary component of the cascade processes of cell death [67]. There is ample evidence that oxidative damage subsidizes significantly to the pathogenesis of neurodegenerative diseases such as HD [60].

3. Apoptosis

There is a link between the pathogenic mechanism of apoptosis and chronic neurodegenerative diseases like HD [61]. Caspases are cysteine-dependent, aspartate-specific proteases that initiate and execute apoptosis. A transcriptional up regulation of caspase-1, caspase-3, and caspase-9 in HD patients as well as in animal models of HD has been reported [62]. Amyloidogenic Mutant Huntingtin (MHtt) has been confirmed to induce apoptosis in HD patients [63].

4. Neuroinflammation

By discharging cell mediators that combat foreign substances and prevent infections, the inflammatory process safeguards our bodies from harm and disease. Neuroinflammation does not directly correlate with HD progression, despite inflammatory processes being evidently confirmed in its pathophysiology. Post-mortem studies of degenerating neurons in HD have discovered high levels of activated microglia and macrophages as well as elevated levels of IL-6, IL-1, and TNF- in the plasma and striatum of HD patients [67]. Microglial cells may identify the pathogenic mHTT aggregates as foreign substances, resulting in neuro-inflammation [64].

5. Neurotoxicity

Disproportionate glutamate neurotransmission leads to excitotoxic neuronal death, which is supplemented by insistent intracellular calcium level elevation [65]. As NMDA (N-Methyl-D-aspartic acid) receptors are over activated by excited amino acids, free radicals are formed and mitochondrial per-

meability transition pores are unlocked, both of which are lethal. The role of neurotoxicity has been documented as significant since the undeviating injection of acids such as QA and kainic acid causes neuro-degeneration of GABAergic MSN in HD [66].

Advances in Huntington's Disease Therapy

The HTT gene mutations that cause HD are still not fully understood, but research on the molecular mechanisms behind them is very promising and could lead to a cure. Currently, there are no neuroprotective therapies that can prevent or slow down the disease, and the only treatments available are symptomatic [67]. One of the main causes of HD is the toxicity of mHTT, the mutant form of the HTT protein, which is produced by the mutated gene. Therefore, reducing the expression of mHTT, either by lowering the levels of HTT mRNA or the protein itself, is a potential strategy to treat HD [68]. Some studies have suggested that gene-silencing techniques that target the CAG repeats in the HTT gene, which are responsible for the mutation, could improve the functional, motor and cognitive outcomes of HD patients, but not their weight loss [67, 69]. These techniques involve using different types of DNA-binding elements, such as zinc-finger proteins, nucleases, epigenetic modulators, or transcription factors, to either block, disrupt, or correct the mutant gene. For example, zinc-finger transcriptional repressors can bind to the DNA and prevent its transcription, while zinc-finger nucleases can cut and edit the DNA [67,70]. Another example of a genome editing technique is CRISPR/Cas9, which can also target and modify the HTT gene. These approaches have the advantage of permanently correcting the CAG expansion that causes HD. Another way of reducing mHTT expression is by using antisense oligonucleotides (ASOs), which are synthetic molecules that bind to the HTT mRNA and trigger its degradation by an enzyme called RNase H1 [71]. ASOs can reach the central nervous system without needing a viral or lipid carrier, and they are easy to develop [67]. A clinical trial by Tabrizi et al [72] used an ASO called IONIS-HTTRx to lower the levels of mHTT in the cerebrospinal fluid of 34 HD patients, who received doses ranging from 10 to 120 mg, and compared them with a placebo group. The results showed that the mHTT reduction was dose-dependent [72]. A similar method of post-transcriptional gene suppression is RNA interference (RNAi), which uses non-coding double-stranded RNA sequences to silence specific genes. RNAi can be achieved by using different types of RNA molecules, such as siRNAs, shRNAs, or artificial miRNAs, which have been shown to reduce the HD symptoms [67]. RNAi is also a promising technique for many other diseases.

One of the main approaches for treating HD is to reduce the synthesis of the mutant HTT (mHTT) protein, which forms toxic aggregates in the brain. This can be achieved by using RNA interference (RNAi) techniques, which involve the use of small RNA molecules that bind to the mHTT mRNA and prevent its translation. Several types of RNA molecules have been used for RNAi, such as short hairpin RNA (shRNA), small interfering RNA (siRNA), and microRNA (miRNA) [67]. These molecules have been delivered to the brain of HD animal models using viral vectors, such as adeno-associated virus (AAV), which contain enhancers and promoters to drive the expression of the RNA molecules. The first trials of RNAi for HD were performed in rodents two decades ago. It is seen that shRNA targeting mHTT reduced its synthesis and prevented the formation of inclusions, gait deficits, and rotarod dysfunction in mice, in recent studies [67]. Similarly,

siRNA injected into the mouse striatum prolonged the survival of striatal neurons, reduced mHTT aggregates, and prevented motor dysfunction [73]. These results were replicated in multiple animal systems, such as rats, monkeys, and sheep [74]. A recent study used a single-stranded siRNA (ss-siRNA) for RNAi and achieved a selective decrease of CAG-expanded HTT protein in various regions of the mouse brain [75]. Another type of RNA molecule that has been used for the suppression of mHTT is miRNA, which is a natural regulator of gene expression. MiRNAs have been shown to have promising effects in genetically modified mice with HD; for example, one study reported that miRNA-mediated knockdown of mHTT prevented regional cortical and striatal atrophy and reduced weight loss [76].

Most of the RNAi techniques do not completely eliminate the production of mHTT, but only reduce it to a certain extent. Therefore, another possible therapeutic approach is to overexpress the wild-type HTT, which may have a protective role against the toxic effects of mHTT. Early trials of this strategy showed that inserting the wild-type HTT into mammalian cells that expressed mHTT reduced cell death [77]. Several natural and synthetic compounds have been suggested as potential candidates for the treatment of HD and other neurodegenerative disorders. One of the most widely studied compounds for HD is tetrabenazine (TBZ), which is an inhibitor of the vesicular monoamine transporter 2 (VMAT2) that blocks the uptake of dopamine into vesicles [67]. TBZ has been shown to exert antichorea effects in patients with HD and was the first approved drug for the disease [78]. However, TBZ has some limitations, such as low bioavailability and adverse effects. Therefore, studies have been conducted to optimize the drug delivery and bioavailability of TBZ using nanotechnology techniques, such as nanoparticles and nanocapsules [79]. Another class of compounds that may have beneficial effects for HD are flavonoids, which are natural polyphenolic compounds found in plants. Flavonoids have been shown to reduce cellular stress and exert anti-inflammatory and anti-apoptotic effects in the cell [80]. Some examples of flavonoids that have been tested for HD are resveratrol, curcumin, and quercetin.

Marine compounds have been proposed as potential sources of novel drugs for HD and other neurodegenerative diseases. Marine compounds have diverse chemical structures and biological activities, such as antioxidant, anti-inflammatory, and anti-apoptotic properties. Some examples of marine compounds that have been investigated for HD are fucoidan, xyloketal B, fucoxanthin, and cerebrosides [67, 81]. A recent study suggested that pridopidine, a dopamine stabilizer, may be a promising drug for HD symptoms. Pridopidine acts on the sigma-1 receptor, which is involved in the regulation of calcium homeostasis, mitochondrial function, and neuroprotection. Pridopidine has been shown to improve motor and cognitive functions in HD animal models and patients [82]. The stage of Huntington's disease (HD) is related to the amount of dopamine in the central nervous system, since dopaminergic conduction disorders are the main cause of HD. Pridopidine, a drug that protects nerve cells from degeneration, has shown promising results in animal models [83]. Drug treatment for HD has the advantage of being based on well-studied active compounds that are effective and tolerable for other similar neurodegenerative diseases [67]. This makes it easier to personalize the medication according to the patient's diagnostics. Another potential treatment for HD is cell replacement therapy using stem cells, which could reduce the symptoms of the disease [84]. Moreover, exercise and physical activity

have been reported to have positive effects on the motor function, gait speed, balance, and social well-being of HD patients [67, 85]. Therefore, exercise could be a complementary therapy for HD. A novel approach to target the underlying cause of HD is the use of monoclonal antibodies that bind to the mutant huntingtin (mHTT) protein and lower its concentration in the cell. This could prevent the mHTT from spreading and causing damage to the brain [84].

Gene therapy: A Possible Treatment of HD in the Future

Research into gene therapy has led to the most exhilarating and favorable advances in HD research. A potential therapy for dominant genetic disorders, silencing mutant genes can offer major benefits. It is generally believed that gene therapy could have a twofold effect: (i) restoring function to non-dead, but dysfunctional neuronal circuits, and (ii) protecting against disease progression [86]. As a matter of fact, gene therapy will not be used to treat disease, but to prevent it - to eliminate symptoms entirely. Molecular gene therapy targets the transcription and translation processes of DNA into mRNA (messenger RNA) by a process called transcription and the synthesis of proteins using the information in mRNA (a process called translation) [87]. Antisense oligonucleotides (ASOs), zinc finger proteins, and RNA interference techniques are three common methods for gene-silencing [88]. Zinc finger proteins suppress transcription, antisense oligonucleotides suppress translation of mHTT, and RNA interference blocks protein translation [89] In large neuroimaging studies performed during preHD, measurable measures of brain regions such as the striatum have been found to be excellent biomarkers of disease progression and will be useful in future gene therapy trials [90].

CONCLUSION

Research indicates that the pathology of Huntington's disease (HD) may be significantly influenced by the loss of function in the normal Htt protein, despite the disease primarily being attributed to a toxic gain of function caused by the expansion of polyglutamine (polyQ) sequences. The Htt protein is known to interact with various effector proteins and is involved in critical cellular processes such as transcription and intracellular trafficking. These interactions and processes are vital for the proper processing and localization of numerous proteins. Consequently, a deficiency in Htt function could potentially have a more extensive impact on cellular physiology than previously comprehended. Given the variety of cellular disruptions caused by this deficiency, it appears that certain neurons may be more resilient than others. Identifying which altered physiological processes most significantly contribute to the progression of HD will be imperative for the development of effective therapeutic interventions. As current therapeutic strategies under development aim to reduce Htt levels, it is also essential to ascertain the degree to which cells can tolerate a reduction in normal Htt expression.

In the field of human disease research, utilizing human subjects is considered the benchmark for validating experimental findings related to disease pathogenesis. This approach is instrumental in elucidating the mechanisms underlying disease onset and in exploring viable treatment modalities for genetic disorders. Take HD, for instance, a genetic condition precipitated by the incessant elongation of the CAG trinucleotide repeat within the Htt gene. The extent of this repeat sequence is a determinant of the age at which HD symptoms manifest, as the accumulation of toxicity from the expanded repeat sequence reaches a critical threshold, instigating cellular damage processes that cul-

minate in neuronal impairment and the onset of the disease. However, the length of the CAG repeat is not static; it is subject to somatic expansion influenced by both genetic and environmental factors. This variability leads to differential susceptibility, damage, and toxicity across various cell types, resulting in diverse phenotypic expressions among individuals. Thus, the DNA repair mechanisms that govern the length of the CAG repeat are pivotal targets for therapeutic interventions aimed at delaying or averting the onset of HD and similar trinucleotide repeat disorders. Nonetheless, these DNA repair mechanisms are modulated by a plethora of genes that serve as modifiers of HD onset, complicating the prediction of disease trajectory for individual patients. Furthermore, these modifier genes may influence not only DNA repair pathways but also other processes that initiate cellular damage and toxicity in HD. Another dimension of HD that remains elusive is the normal function of the Htt protein, which is implicated in synaptic vesicle trafficking and endosomal signaling—processes that are crucial for neuronal development and functionality. The precise mechanisms by which Htt facilitates these synaptic functions, and how they are disrupted by the mutant form of Htt in HD-afflicted neurons, are areas that warrant further investigation. A more thorough characterization of the normal roles of Htt could unveil new therapeutic avenues and foster a more holistic understanding of HD.
.

AUTHOR INFORMATION

Corresponding Author

Neelabh Datta - neelabhdatta@gmail.com

Author Contributions

Text.

REFERENCES

[1] Myers, R. H., MacDonald, M. E., Koroshetz, W. J., Duyao, M. P., Ambrose, C. M., Taylor, S. A., Barnes, G., Srinidhi, J., Lin, C. S., & Whaley, W. L. (1993). De novo expansion of a (CAG)n repeat in sporadic Huntington's disease. Nature genetics, 5(2), 168–173. https://doi.org/10.1038/ng1093-168.

[2] Schulte, J., & Littleton, J. T. (2011). The biological function of the Huntingtin protein and its relevance to Huntington's Disease pathology. Current trends in neurology, 5, 65–78.

[3] Myers R. H. (2004). Huntington's disease genetics. NeuroRx : the journal of the American Society for Experimental NeuroTherapeutics, 1(2), 255–262. https://doi.org/10.1602/neurorx.1.2.255.

[4] Squitieri, F., Cannella, M., & Simonelli, M. (2002). CAG mutation effect on rate of progression in Huntington's disease. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, 23 Suppl 2, S107–S108. https://doi.org/10.1007/s100720200092

[5] Rubinsztein, D. C., Leggo, J., Chiano, M., Korn, S., Dodge, A., Norbury, G., Rosser, E., & Craufurd, D. (1997). Homozygotes and heterozygotes for ciliary neurotrophic factor null alleles do not show earlier onset of Huntington's disease. Neurology, 49(3), 890–892. https://doi.org/10.1212/wnl.49.3.890.

[6] Albin, R. L., Reiner, A., Anderson, K. D., Dure, L. S., 4th, Handelin, B., Balfour, R., Whetsell, W. O., Jr, Penney, J. B., & Young, A. B. (1992). Preferential loss of striato-external pallidal projection neurons in presymptomatic Huntington's disease. Annals of neurology, 31(4), 425–430. https://doi.org/10.1002/ana.410310412.

[7] Sapp, E., Kegel, K. B., Aronin, N., Hashikawa, T., Uchiyama, Y., Tohyama, K., Bhide, P. G., Vonsattel, J. P., & DiFiglia, M. (2001). Early and progressive accumulation of reactive microglia in the Huntington disease brain. Journal of neuropathology and experimental neurology, 60(2), 161–172. https://doi.org/10.1093/jnen/60.2.161.

[8] Vonsattel, J. P., Myers, R. H., Stevens, T. J., Ferrante, R. J., Bird, E. D., & Richardson, E. P., Jr (1985). Neuropathological classification of Huntington's disease. Journal of neuropathology and experimental neurology, 44(6), 559–577. https://doi.org/10.1097/00005072-198511000-00003.

[9] Nopoulos, P. C., Aylward, E. H., Ross, C. A., Johnson, H. J., Magnotta, V. A., Juhl, A. R., Pierson, R. K., Mills, J., Langbehn, D. R., Paulsen, J. S., & PREDICT-HD Investigators Coordinators of Huntington Study Group (HSG) (2010). Cerebral cortex structure in prodromal Huntington disease. Neurobiology of disease, 40(3), 544–554. https://doi.org/10.1016/j.nbd.2010.07.014.

[10] Squitieri, F., Cannella, M., Simonelli, M., Sassone, J., Martino, T., Venditti, E., Ciammola, A., Colonnese, C., Frati, L., & Ciarmiello, A. (2009). Distinct brain volume changes correlating with clinical stage, disease progression rate, mutation size, and age at onset prediction as early biomarkers of brain atrophy in Huntington's disease. CNS neuroscience & therapeutics, 15(1), 1–11. https://doi.org/10.1111/j.1755-5949.2008.00068.x.

[11] de la Monte, S. M., Vonsattel, J. P., & Richardson, E. P., Jr (1988). Morphometric demonstration of atrophic changes in the cerebral cortex, white matter, and neostriatum in Huntington's disease. Journal of neuropathology and experimental neurology, 47(5), 516–525. https://doi.org/10.1097/00005072-198809000-00003.

[12] Hatters D. M. (2008). Protein misfolding inside cells: the case of huntingtin and Huntington's disease. IUBMB life, 60(11), 724–728. https://doi.org/10.1002/iub.111.

[13] Scherzinger, E., Sittler, A., Schweiger, K., Heiser, V., Lurz, R., Hasenbank, R., Bates, G. P., Lehrach, H., & Wanker, E. E. (1999). Self-assembly of polyglutamine-containing huntingtin fragments into amyloid-like fibrils: implications for Huntington's disease pathology. Proceedings of the National Academy of Sciences of the United States of America, 96(8), 4604–4609. https://doi.org/10.1073/pnas.96.8.4604.

[14] Nucifora , F. C., Jr, Sasaki, M., Peters, M. F., Huang, H., Cooper, J. K., Yamada, M., Takahashi, H., Tsuji, S., Troncoso, J., Dawson, V. L., Dawson, T. M., & Ross, C. A. (2001). Interference by huntingtin and atrophin-1 with cbp-mediated transcription leading to cellular toxicity. Science (New York, N.Y.), 291(5512), 2423–2428. https://doi.org/10.1126/science.1056784.

[15] Imarisio, S., Carmichael, J., Korolchuk, V., Chen, C. W., Saiki, S., Rose, C., Krishna, G., Davies, J. E., Ttofi, E., Underwood, B. R., & Rubinsztein, D. C. (2008). Huntington's disease: from pathology and genetics to potential therapies. The Biochemical journal, 412(2), 191–209. https://doi.org/10.1042/BJ20071619.

[16] Baxendale, S., Abdulla, S., Elgar, G., Buck, D., Berks, M., Micklem, G., Durbin, R., Bates, G., Brenner, S., & Beck, S. (1995). Comparative sequence analysis of the human and pufferfish Huntington's disease genes. Nature genetics, 10(1), 67–76. https://doi.org/10.1038/ng0595-67.

[17] Li, W., Serpell, L. C., Carter, W. J., Rubinsztein, D. C., & Huntington, J. A. (2006). Expression and characterization of full-length human huntingtin, an elongated HEAT repeat protein. The Journal of biological chemistry, 281(23), 15916–15922. https://doi.org/10.1074/jbc.M511007200.

[18] MacDonald M. E. (2003). Huntingtin: alive and well and working in middle management. Science's STKE : signal transduction knowledge environment, 2003(207), pe48. https://doi.org/10.1126/stke.2003.207.pe48.

[19] Myers RH, Marans K, MacDonald ME. Huntington's disease. In: Genetic instabilities and hereditary neurological diseases (Warren ST, Wells RT, eds), pp 301–323. New York: Academic Press, 1998.

[20] Gusella, J. F., Wexler, N. S., Conneally, P. M., Naylor, S. L., Anderson, M. A., Tanzi, R. E., Watkins, P. C., Ottina, K., Wallace, M. R., & Sakaguchi, A. Y. (1983). A polymorphic DNA marker genetically linked to Huntington's disease. Nature, 306(5940), 234–238. https://doi.org/10.1038/306234a0.

[21] Myers R. H. (2004). Huntington's disease genetics. NeuroRx : the journal of the American Society for Experimental NeuroTherapeutics, 1(2), 255–262. https://doi.org/10.1602/neurorx.1.2.255.

[22] Duyao, M., Ambrose, C., Myers, R., Novelletto, A., Persichetti, F., Frontali, M., Folstein, S., Ross, C., Franz, M., & Abbott, M. (1993). Trinucleotide repeat length instability and age of onset in Huntington's disease. Nature genetics, 4(4), 387–392. https://doi.org/10.1038/ng0893-387.

[23] Tartari, M., Gissi, C., Lo Sardo, V., Zuccato, C., Picardi, E., Pesole, G., & Cattaneo, E. (2008). Phylogenetic comparison of huntingtin homologues reveals the appearance of a primitive polyQ in sea urchin. Molecular biology and evolution, 25(2), 330–338. https://doi.org/10.1093/molbev/msm258.

[24] Takano, H., & Gusella, J. F. (2002). The predominantly HEAT-like motif structure of huntingtin and its association and coincident nuclear entry with dorsal, an NF-kB/Rel/dorsal family transcription factor. BMC neuroscience, 3, 15. https://doi.org/10.1186/1471-2202-3-15.

[25] Chook, Y. M., & Blobel, G. (1999). Structure of the nuclear transport complex karyopherin-beta2-Ran x GppNHp. Nature, 399(6733), 230–237. https://doi.org/10.1038/20375.

[26] Grinthal, A., Adamovic, I., Weiner, B., Karplus, M., & Kleckner, N. (2010). PR65, the HEAT-repeat scaffold of phosphatase PP2A, is an elastic connector that links force and catalysis. Proceedings of the National Academy of Sciences of the United States of America, 107(6), 2467–2472. https://doi.org/10.1073/pnas.0914073107.

[27] Tartari, M., Gissi, C., Lo Sardo, V., Zuccato, C., Picardi, E., Pesole, G., & Cattaneo, E. (2008). Phylogenetic comparison of huntingtin homologues reveals the appearance of a primitive polyQ in sea urchin. Molecular biology and evolution, 25(2), 330–338. https://doi.org/10.1093/molbev/msm258.

[28] Li, S. H., & Li, X. J. (2004). Huntingtin-protein interactions and the pathogenesis of Huntington's disease. Trends in genetics : TIG, 20(3), 146–154. https://doi.org/10.1016/j.tig.2004.01.008.

[29] Clabough, E. B., & Zeitlin, S. O. (2006). Deletion of the triplet repeat encoding polyglutamine within the mouse Huntington's disease gene results in subtle behavior-

al/motor phenotypes in vivo and elevated levels of ATP with cellular senescence in vitro. Human molecular genetics, 15(4), 607–623. https://doi.org/10.1093/hmg/ddi477.

[30] Fiumara, F., Fioriti, L., Kandel, E. R., & Hendrickson, W. A. (2010). Essential role of coiled coils for aggregation and activity of Q/N-rich prions and PolyQ proteins. Cell, 143(7), 1121–1135. https://doi.org/10.1016/j.cell.2010.11.042.

[31] Ignatova, Z., & Gierasch, L. M. (2006). Inhibition of protein aggregation in vitro and in vivo by a natural osmoprotectant. Proceedings of the National Academy of Sciences of the United States of America, 103(36), 13357–13361. https://doi.org/10.1073/pnas.0603772103.

[32] Qin, Z. H., Wang, Y., Sapp, E., Cuiffo, B., Wanker, E., Hayden, M. R., Kegel, K. B., Aronin, N., & DiFiglia, M. (2004). Huntingtin bodies sequester vesicle-associated proteins by a polyproline-dependent interaction. The Journal of neuroscience : the official journal of the Society for Neuroscience, 24(1), 269–281. https://doi.org/10.1523/JNEUROSCI.1409-03.2004.

[33] Atwal, R. S., Xia, J., Pinchev, D., Taylor, J., Epand, R. M., & Truant, R. (2007). Huntingtin has a membrane association signal that can modulate huntingtin aggregation, nuclear entry and toxicity. Human molecular genetics, 16(21), 2600–2615. https://doi.org/10.1093/hmg/ddm217.

[34] Cornett, J., Cao, F., Wang, C. E., Ross, C. A., Bates, G. P., Li, S. H., & Li, X. J. (2005). Polyglutamine expansion of huntingtin impairs its nuclear export. Nature genetics, 37(2), 198–204. https://doi.org/10.1038/ng1503.

[35] Gafni, J., Hermel, E., Young, J. E., Wellington, C. L., Hayden, M. R., & Ellerby, L. M. (2004). Inhibition of calpain cleavage of huntingtin reduces toxicity: accumulation of calpain/caspase fragments in the nucleus. The Journal of biological chemistry, 279(19), 20211–20220. https://doi.org/10.1074/jbc.M401267200.

[36] Mende-Mueller, L. M., Toneff, T., Hwang, S. R., Chesselet, M. F., & Hook, V. Y. (2001). Tissue-specific proteolysis of Huntingtin (htt) in human brain: evidence of enhanced levels of N- and C-terminal Htt fragments in Huntington's disease striatum. The Journal of neuroscience : the official journal of the Society for Neuroscience, 21(6), 1830–1837. https://doi.org/10.1523/JNEUROSCI.21-06-01830.2001.

[37] Kim, Y. J., Sapp, E., Cuiffo, B. G., Sobin, L., Yoder, J., Kegel, K. B., Qin, Z. H., Detloff, P., Aronin, N., & DiFiglia, M. (2006). Lysosomal proteases are involved in generation of N-terminal huntingtin fragments. Neurobiology of disease, 22(2), 346–356. https://doi.org/10.1016/j.nbd.2005.11.012.

[38] Humbert, S., Bryson, E. A., Cordelières, F. P., Connors, N. C., Datta, S. R., Finkbeiner, S., Greenberg, M. E., & Saudou, F. (2002). The IGF-1/Akt pathway is neuroprotective in Huntington's disease and involves Huntingtin phosphorylation by Akt. Developmental cell, 2(6), 831–837. https://doi.org/10.1016/s1534-5807(02)00188-0.

[39] Metzler, M., Gan, L., Mazarei, G., Graham, R. K., Liu, L., Bissada, N., Lu, G., Leavitt, B. R., & Hayden, M. R. (2010). Phosphorylation of huntingtin at Ser421 in YAC128 neurons is associated with protection of YAC128 neurons from NMDA-mediated excitotoxicity and is modulated by

PP1 and PP2A. The Journal of neuroscience : the official journal of the Society for Neuroscience, 30(43), 14318–14329. https://doi.org/10.1523/JNEUROSCI.1589-10.2010.

[40] Yanai, A., Huang, K., Kang, R., Singaraja, R. R., Arstikaitis, P., Gan, L., Orban, P. C., Mullard, A., Cowan, C. M., Raymond, L. A., Drisdel, R. C., Green, W. N., Ravikumar, B., Rubinsztein, D. C., El-Husseini, A., & Hayden, M. R. (2006). Palmitoylation of huntingtin by HIP14 is essential for its trafficking and function. Nature neuroscience, 9(6), 824–831. https://doi.org/10.1038/nn1702.

[41] DiFiglia, M., Sapp, E., Chase, K., Schwarz, C., Meloni, A., Young, C., Martin, E., Vonsattel, J. P., Carraway, R., & Reeves, S. A. (1995). Huntingtin is a cytoplasmic protein associated with vesicles in human and rat brain neurons. Neuron, 14(5), 1075–1081. https://doi.org/10.1016/0896-6273(95)90346-1.

[42] Hebb, M. O., Denovan-Wright, E. M., & Robertson, H. A. (1999). Expression of the Huntington's disease gene is regulated in astrocytes in the arcuate nucleus of the hypothalamus of postpartum rats. FASEB journal : official publication of the Federation of American Societies for Experimental Biology, 13(9), 1099–1106. https://doi.org/10.1096/fasebj.13.9.1099.

[43] Ko, J., Ou, S., & Patterson, P. H. (2001). New anti-huntingtin monoclonal antibodies: implications for huntingtin conformation and its binding proteins. Brain research bulletin, 56(3-4), 319–329. https://doi.org/10.1016/s0361-9230(01)00599-8.

[44] Borrell-Pagès, M., Zala, D., Humbert, S., & Saudou, F. (2006). Huntington's disease: from huntingtin function and dysfunction to therapeutic strategies. Cellular and molecular life sciences : CMLS, 63(22), 2642–2660. https://doi.org/10.1007/s00018-006-6242-0.

[45] Semaka, A., Creighton, S., Warby, S., & Hayden, M. R. (2006). Predictive testing for Huntington disease: interpretation and significance of intermediate alleles. Clinical genetics, 70(4), 283–294. https://doi.org/10.1111/j.1399-0004.2006.00668.x.

[46] S. Mahalingam and L.M. Levy (2014). Genetics of Huntington Disease American Journal of Neuroradiology 35 (6) 1070-1072; DOI: https://doi.org/10.3174/ajnr.A3772.

[47] Walker F. O. (2007). Huntington's disease. Lancet (London, England), 369(9557), 218–228. https://doi.org/10.1016/S0140-6736(07)60111-1.

[48] Tabrizi, S. J., Langbehn, D. R., Leavitt, B. R., Roos, R. A., Durr, A., Craufurd, D., Kennard, C., Hicks, S. L., Fox, N. C., Scahill, R. I., Borowsky, B., Tobin, A. J., Rosas, H. D., Johnson, H., Reilmann, R., Landwehrmeyer, B., Stout, J. C., & TRACK-HD investigators (2009). Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. The Lancet. Neurology, 8(9), 791–801. https://doi.org/10.1016/S1474-4422(09)70170-X.

[49] Trottier, Y., Devys, D., Imbert, G., Saudou, F., An, I., Lutz, Y., Weber, C., Agid, Y., Hirsch, E. C., & Mandel, J. L. (1995). Cellular localization of the Huntington's disease protein and discrimination of the normal and mutated form. Nature genetics, 10(1), 104–110. https://doi.org/10.1038/ng0595-104.

[50] Bates G. (2003). Huntingtin aggregation and toxicity in Huntington's disease. Lancet (London, England), 361(9369), 1642–1644.

https://doi.org/10.1016/S0140-6736(03)13304-1.

[51] Ross, C. A., & Tabrizi, S. J. (2011). Huntington's disease: from molecular pathogenesis to clinical treatment. The Lancet. Neurology, 10(1), 83–98. https://doi.org/10.1016/S1474-4422(10)70245-3.

[52] Walker F. O. (2007). Huntington's disease. Lancet (London, England), 369(9557), 218–228. https://doi.org/10.1016/S0140-6736(07)60111-1.

[53] Koutsis G, Karadima G, Kladi A, et al. (2013). The challenge of juvenile Huntington disease: to test or not to test. Neurology; 80:990–96.

[54] Gusella, J. F., MacDonald, M. E., & Lee, J. M. (2014). Genetic modifiers of Huntington's disease. Movement disorders : official journal of the Movement Disorder Society, 29(11), 1359–1365. https://doi.org/10.1002/mds.26001.

[55] Hong, E. P., MacDonald, M. E., Wheeler, V. C., Jones, L., Holmans, P., Orth, M., Monckton, D. G., Long, J. D., Kwak, S., Gusella, J. F., & Lee, J. M. (2021). Huntington's Disease Pathogenesis: Two Sequential Components. Journal of Huntington's disease, 10(1), 35–51. https://doi.org/10.3233/JHD-200427.

[56] Lee, J. M., Ramos, E. M., Lee, J. H., Gillis, T., Mysore, J. S., Hayden, M. R., Warby, S. C., Morrison, P., Nance, M., Ross, C. A., Margolis, R. L., Squitieri, F., Orobello, S., Di Donato, S., Gomez-Tortosa, E., Ayuso, C., Suchowersky, O., Trent, R. J., McCusker, E., Novelletto, A., … COHORT study of the HSG (2012). CAG repeat expansion in Huntington disease determines age at onset in a fully dominant fashion. Neurology, 78(10), 690–695. https://doi.org/10.1212/WNL.0b013e318249f683.

[57] Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium (2015). Identification of Genetic Factors that Modify Clinical Onset of Huntington's Disease. Cell, 162(3), 516–526. https://doi.org/10.1016/j.cell.2015.07.003.

[58] Lee, J. M., Gillis, T., Mysore, J. S., Ramos, E. M., Myers, R. H., Hayden, M. R., Morrison, P. J., Nance, M., Ross, C. A., Margolis, R. L., Squitieri, F., Griguoli, A., Di Donato, S., Gomez-Tortosa, E., Ayuso, C., Suchowersky, O., Trent, R. J., McCusker, E., Novelletto, A., Frontali, M., … Gusella, J. F. (2012). Common SNP-based haplotype analysis of the 4p16.3 Huntington disease gene region. American journal of human genetics, 90(3), 434–444. https://doi.org/10.1016/j.ajhg.2012.01.005.

[59] Quintanilla, R. A., & Johnson, G. V. (2009). Role of mitochondrial dysfunction in the pathogenesis of Huntington's disease. Brain research bulletin, 80(4-5), 242–247. https://doi.org/10.1016/j.brainresbull.2009.07.010.

[60] Chen C. M. (2011). Mitochondrial dysfunction, metabolic deficits, and increased oxidative stress in Huntington's disease. Chang Gung medical journal, 34(2), 135–152.

[61] Friedlander R. M. (2003). Apoptosis and caspases in neurodegenerative diseases. The New England journal of medicine, 348(14), 1365–1375. https://doi.org/10.1056/NEJMra022366.

[62] Leegwater-Kim, J., & Cha, J. H. (2004). The paradigm of Huntington's disease: therapeutic opportunities in neurodegeneration. NeuroRx : the journal of the American Society for Experimental NeuroTherapeutics, 1(1),

128–138. https://doi.org/10.1602/neurorx.1.1.128.

[63] Li, S. H., Lam, S., Cheng, A. L., & Li, X. J. (2000). Intranuclear huntingtin increases the expression of caspase-1 and induces apoptosis. Human molecular genetics, 9(19), 2859–2867. https://doi.org/10.1093/hmg/9.19.2859.

[64] Kalonia, H., Kumar, P., & Kumar, A. (2011). Attenuation of proinflammatory cytokines and apoptotic process by verapamil and diltiazem against quinolinic acid induced Huntington like alterations in rats. Brain research, 1372, 115–126. https://doi.org/10.1016/j.brainres.2010.11.060.

[65] DiFiglia M. (1990). Excitotoxic injury of the neostriatum: a model for Huntington's disease. Trends in neurosciences, 13(7), 286–289. https://doi.org/10.1016/0166-2236(90)90111-m.

[66] Jamwal, S., & Kumar, P. (2015). Antidepressants for neuroprotection in Huntington's disease: A review. European journal of pharmacology, 769, 33–42. https://doi.org/10.1016/j.ejphar.2015.10.033.

[67] Palaiogeorgou, A.M., Papakonstantinou, E., Golfinopoulou, R., Sigala, M., Mitsis, T., Papageorgiou, L. ... Vlachakis, D. (2023). Recent approaches on Huntington's disease (Review). Biomedical Reports, 18, 5. https://doi.org/10.3892/br.2022.1587

[68] Barker, R. A., Fujimaki, M., Rogers, P., & Rubinsztein, D. C. (2020). Huntingtin-lowering strategies for Huntington's disease. Expert opinion on investigational drugs, 29(10), 1125–1132. https://doi.org/10.1080/13543784.2020.1804552

[69] Aziz, N. A., van der Burg, J. M. M., Tabrizi, S. J., & Landwehrmeyer, G. B. (2018). Overlap between age-at-onset and disease-progression determinants in Huntington disease. Neurology, 90(24), e2099–e2106. https://doi.org/10.1212/WNL.0000000000005690

[70] Tabrizi, S. J., Ghosh, R., & Leavitt, B. R. (2019). Huntingtin Lowering Strategies for Disease Modification in Huntington's Disease. Neuron, 102(4), 899. https://doi.org/10.1016/j.neuron.2019.05.001

[71] Lane, R. M., Smith, A., Baumann, T., Gleichmann, M., Norris, D., Bennett, C. F., & Kordasiewicz, H. (2018). Translating Antisense Technology into a Treatment for Huntington's Disease. Methods in molecular biology (Clifton, N.J.), 1780, 497–523. https://doi.org/10.1007/978-1-4939-7825-0_23

[72] Tabrizi, S. J., Leavitt, B. R., Landwehrmeyer, G. B., Wild, E. J., Saft, C., Barker, R. A., Blair, N. F., Craufurd, D., Priller, J., Rickards, H., Rosser, A., Kordasiewicz, H. B., Czech, C., Swayze, E. E., Norris, D. A., Baumann, T., Gerlach, I., Schobel, S. A., Paz, E., Smith, A. V., … Phase 1–2a IONIS-HTTRx Study Site Teams (2019). Targeting Huntingtin Expression in Patients with Huntington's Disease. The New England journal of medicine, 380(24), 2307–2316. https://doi.org/10.1056/NEJMoa1900907

[73] Keiser, M. S., Kordasiewicz, H. B., & McBride, J. L. (2016). Gene suppression strategies for dominantly inherited neurodegenerative diseases: lessons from Huntington's disease and spinocerebellar ataxia. Human molecular genetics, 25(R1), R53–R64. https://doi.org/10.1093/hmg/ddv442

[74] DiFiglia, M., Sena-Esteves, M., Chase, K., Sapp, E., Pfister, E., Sass, M., Yoder, J., Reeves, P., Pandey, R. K., Rajeev, K. G.,

Manoharan, M., Sah, D. W., Zamore, P. D., & Aronin, N. (2007). Therapeutic silencing of mutant huntingtin with siRNA attenuates striatal and cortical neuropathology and behavioral deficits. Proceedings of the National Academy of Sciences of the United States of America, 104(43), 17204–17209. https://doi.org/10.1073/pnas.0708285104

[75] Yu, D., Pendergraff, H., Liu, J., Kordasiewicz, H. B., Cleveland, D. W., Swayze, E. E., Lima, W. F., Crooke, S. T., Prakash, T. P., & Corey, D. R. (2012). Single-stranded RNAs use RNAi to potently and allele-selectively inhibit mutant huntingtin expression. Cell, 150(5), 895–908. https://doi.org/10.1016/j.cell.2012.08.002

[76] Dufour, B. D., Smith, C. A., Clark, R. L., Walker, T. R., & McBride, J. L. (2014). Intrajugular vein delivery of AAV9-RNAi prevents neuropathological changes and weight loss in Huntington's disease mice. Molecular therapy : the journal of the American Society of Gene Therapy, 22(4), 797–810. https://doi.org/10.1038/mt.2013.289

[77] Ho, L. W., Brown, R., Maxwell, M., Wyttenbach, A., & Rubinsztein, D. C. (2001). Wild type Huntingtin reduces the cellular toxicity of mutant Huntingtin in mammalian cell models of Huntington's disease. Journal of medical genetics, 38(7), 450–452. https://doi.org/10.1136/jmg.38.7.450

[78] Huntington Study Group (2006). Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. Neurology, 66(3), 366–372. https://doi.org/10.1212/01.wnl.0000198586.85250.13

[79] Arora, A., Kumar, S., Ali, J., & Baboota, S. (2020). Intranasal delivery of tetrabenazine nanoemulsion via olfactory region for better treatment of hyperkinetic movement associated with Huntington's disease: Pharmacokinetic and brain delivery study. Chemistry and physics of lipids, 230, 104917. https://doi.org/10.1016/j.chemphyslip.2020.104917

[80] Devi, S., Kumar, V., Singh, S. K., Dubey, A. K., & Kim, J. J. (2021). Flavonoids: Potential Candidates for the Treatment of Neurodegenerative Disorders. Biomedicines, 9(2), 99. https://doi.org/10.3390/biomedicines9020099

[81] Catanesi, M., Caioni, G., Castelli, V., Benedetti, E., d'Angelo, M., & Cimini, A. (2021). Benefits under the Sea: The Role of Marine Compounds in Neurodegenerative Disorders. Marine drugs, 19(1), 24. https://doi.org/10.3390/md19010024

[82] Jabłońska, M., Grzelakowska, K., Wiśniewski, B., Mazur, E., Leis, K., & Gałązka, P. (2020). Pridopidine in the treatment of Huntington's disease. Reviews in the neurosciences, 31(4), 441–451. https://doi.org/10.1515/revneuro-2019-0085

[83] Garcia-Miralles, M., Geva, M., Tan, J. Y., Yusof, N. A. B. M., Cha, Y., Kusko, R., Tan, L. J., Xu, X., Grossman, I., Orbach, A., Hayden, M. R., & Pouladi, M. A. (2017). Early pridopidine treatment improves behavioral and transcriptional deficits in YAC128 Huntington disease mice. JCI insight, 2(23), e95665. https://doi.org/10.1172/jci.insight.95665

[84] Bartl, S., Oueslati, A., Southwell, A. L., Siddu, A., Parth, M., David, L. S., Maxan, A., Salhat, N., Burkert, M., Mairhofer, A., Friedrich, T., Pankevych, H., Balazs, K., Staffler, G., Hayden, M. R., Cicchetti, F., & Smrzka, O. W. (2020). Inhibiting cellular uptake of mutant huntingtin using a monoclonal antibody: Implications for the treatment of Huntington's disease. Neurobiology of disease, 141, 104943. https://doi.org/10.1016/j.nbd.2020.104943

[85] Fritz, N. E., Rao, A. K., Kegelmeyer, D., Kloos, A., Busse, M., Hartel, L., Carrier, J., & Quinn, L. (2017). Physical Therapy and Exercise Interventions in Huntington's Disease: A Mixed Methods Systematic Review. Journal of Huntington's disease, 6(3), 217–235. https://doi.org/10.3233/JHD-170260

[86] Nopoulos P. C. (2016). Huntington disease: a single-gene degenerative disorder of the striatum. Dialogues in clinical neuroscience, 18(1), 91–98. https://doi.org/10.31887/DCNS.2016.18.1/pnopoulos.

[87] Shannon, K. M., & Fraint, A. (2015). Therapeutic advances in Huntington's Disease. Movement disorders : official journal of the Movement Disorder Society, 30(11), 1539–1546. https://doi.org/10.1002/mds.26331.

[88] Paulsen, J. S., Long, J. D., Johnson, H. J., Aylward, E. H., Ross, C. A., Williams, J. K., Nance, M. A., Erwin, C. J., Westervelt, H. J., Harrington, D. L., Bockholt, H. J., Zhang, Y., McCusker, E. A., Chiu, E. M., Panegyres, P. K., & PREDICT-HD Investigators and Coordinators of the Huntington Study Group (2014). Clinical and Biomarker Changes in Premanifest Huntington Disease Show Trial Feasibility: A Decade of the PREDICT-HD Study. Frontiers in aging neuroscience, 6, 78. https://doi.org/10.3389/fnagi.2014.00078.

[89] Maxwell M. M. (2009). RNAi applications in therapy development for neurodegenerative disease. Current pharmaceutical design, 15(34), 3977–3991. https://doi.org/10.2174/138161209789649295.

[90] Beal, M. F., Ferrante, R. J., Swartz, K. J., & Kowall, N. W. (1991). Chronic quinolinic acid lesions in rats closely resemble Huntington's disease. The Journal of neuroscience : the official journal of the Society for Neuroscience, 11(6), 1649–1659. https://doi.org/10.1523/JNEUROSCI.11-06-01649.1991.

[91] Rozas, J. L., Gómez-Sánchez, L., Tomás-Zapico, C., Lucas, J. J., & Fernández-Chacón, R. (2010). Presynaptic dysfunction in Huntington's disease. Biochemical Society transactions, 38(2), 488–492. https://doi.org/10.1042/BST0380488.

[92] von Zastrow, M., & Sorkin, A. (2007). Signaling on the endocytic pathway. Current opinion in cell biology, 19(4), 436–445. https://doi.org/10.1016/j.ceb.2007.04.021.

[93] Hong, E. P., MacDonald, M. E., Wheeler, V. C., Jones, L., Holmans, P., Orth, M., Monckton, D. G., Long, J. D., Kwak, S., Gusella, J. F., & Lee, J. M. (2021). Huntington's Disease Pathogenesis: Two Sequential Components. Journal of Huntington's disease, 10(1), 35–51. https://doi.org/10.3233/JHD-200427.