Non-Cell Autonomous and Epigenetic Mechanisms of Huntington’s Disease

Chaebin Kim 1,†, Ali Yousefian-Jazi 1,†, Seung-Hye Choi 1, Inyoung Chang 2, Junghhee Lee 3,4,5,* and Hoon Ryu 1,*

1 Brain Science Institute, Korea Institute of Science and Technology, Seoul 02792, Korea; cbkim@kist.re.kr (C.K.); yousefian@kist.re.kr (A.Y.-J.); shchoi323@kist.re.kr (S.-H.C.)
2 Department of Biology, Boston University, Boston, MA 02215, USA; ic313@bu.edu
3 Boston University Alzheimer’s Disease Research Center, Boston University, Boston, MA 02118, USA
4 Department of Neurology, Boston University School of Medicine, Boston, MA 02118, USA
5 VA Boston Healthcare System, Boston, MA 02130, USA
* Correspondence: junghee@bu.edu; Tel.: +1-857-364-6034 (J.L.); hoonryu@kist.re.kr; Tel.: +82-2-958-6855 (H.R.)
† These authors equally contributed to this review.

Abstract: Huntington’s disease (HD) is a rare neurodegenerative disorder caused by an expansion of CAG trinucleotide repeat located in the exon 1 of Huntingtin (HTT) gene in human chromosome 4. The HTT protein is ubiquitously expressed in the brain. Specifically, mutant HTT (mHTT) protein-mediated toxicity leads to a dramatic degeneration of the striatum among many regions of the brain. HD symptoms exhibit a major involuntary movement followed by cognitive and psychiatric dysfunctions. In this review, we address the conventional role of wild type HTT (wtHTT) and how mHTT modulates epigenetic modifications and transcriptional pathways in MSNs. We also discuss how non-cell autonomous pathways lead to damage and death of MSNs under HD pathological conditions. Lastly, we overview therapeutic approaches for HD. Together, understanding of precise neuropathological mechanisms of HD may improve therapeutic approaches to treat the onset and progression of HD.

Keywords: Huntington’s disease; non-cell autonomous pathway; astrocyte; oligodendrocyte; epigenetics; mitochondria dysfunction; vesicle trafficking; therapeutic targets

1. Introduction

Huntington’s disease (HD) is a fatal progressive neurodegenerative disorder with a mid-life onset which ranges from infancy to the ninth decade. HD occurs in 5–10 cases per 100,000 persons worldwide, and characterized by chorea, emotional distress, and progressive cognitive decline [1]. Generally, in HD patients, there are more than 38 repeats of trinucleotide CAG within the Huntingtin (HTT) gene with an inverse relationship between the number of CAG repeats and the age of onset, indicating that the high number of CAG repeats cause the earlier phenotype of HD symptoms [2–4]. HTT has a crucial role in embryonic development by showing the death of embryos of huntingtin homozygous knockout mice by day 7.5 [5]. On the other hand, HTT plays an important role in cardiomyocytes cellular energy and nucleotides metabolism [6].

Currently, HD is considered as a multi-systemic neurodegenerative disease due to skeletal muscle and heart function disturbances with energy metabolism and mitochondrial alterations beyond the brain dysfunction [7]. Although most of studies show intracellular inclusions formed by mutant HTT (mHTT) protein in selected regions of the brain such as the striatum and cortex of HD brain [8,9], other studies find the expression and function of mHTT in skeletal muscle and heart as well [10]. The mHTT is involved in transcriptional alterations, disruption of intracellular transport, excitotoxicity, collapse of protein degradation mechanisms, mitochondrial dysfunction, and disorders of myelin, which make
neurons more susceptible to generic stresses, eventually leading to neuronal death [11–14]. Yamanishi et al. have reported a novel cell death pathway known as transcriptional repression-induced atypical cell death of neurons (TRIAD) in the HD pathology, exhibiting that enlargement of endoplasmic reticulum (ER) contributes to neuronal cell damage without alteration of mitochondria and nuclei structure [15]. Another study has shown that inflammation may play a role in cardiac dysfunction in HD by overexpression of the inflammatory cytokine, tumor necrosis factor-α, in cardiomyocytes of R6/2 HD mice [16].

The epigenetic modifications are closely associated with the pathogenesis of HD [17,18]. mHTT sequesters specific transcription factors and impairs their function, resulting in disruption of their target genes transcription [19–21]. mHTT also regulates transcription by facilitating transcriptional factor interaction with protein complexes [22]. Otherwise, mHTT leads to histone hypoacetylation which can change genes expressions [23–25]. Moreover, several studies have shown that the biochemical defect and impairment of neuronal energy metabolism in HD patients are caused by mitochondrial dysfunction, where mitochondria is a major contributor of energy production and a regulator of intracellular signaling and survival [26,27]. The calcium-ion (Ca²⁺) buffering abnormalities and bioenergetic impairments in mitochondria can occur by interaction of mHTT with mitochondrial proteins [28–30]. Recently, researchers have become more interested in identifying the roles of non-neuronal cells in HD pathophysiology through elucidation of alterations in oligodendrocyte functions such as myelin formation [31–33] and astrocyte morphological changes and functions including impairment of glutamate metabolism and potassium homeostasis [34–36]. In this review, we discuss how astrocytes and oligodendrocytes contribute to HD pathogenesis via a non-cell autonomous pathway. Furthermore, we review the different epigenetic modifications which have key roles in neurotoxicity and neurogenesis impairment, and finally discuss potential therapeutic strategies for HD.

2. Non-Cell Autonomous Cell Death Pathway in HD

While the primary causes of neuronal damage and cell death are abnormalities within the damaged neuron itself, other neighboring cells such as glial cells also contribute to neuronal death [37,38]. In this regard, non-cell autonomous pathway is defined in this review as the mechanism of the neuronal damage caused by non-neuronal cells. Recent studies have proven the non-cell autonomous pathway in that reactive astrocytes lead to neuronal damage and neurodegeneration in Alzheimer’s disease (AD), amyotrophic lateral sclerosis (ALS), HD, and Parkinson’s disease (PD) [39–42]. Indeed, neuron-specific expression of mHTT in the striatum and cortex is not sufficient to fully induce pathological phenotypes of HD [43]. Otherwise, astrocyte-specific expression of mHTT does not induce neurodegeneration, but it shows neurological symptoms [44]. In the HD fly model (UAS HttQ100-mRFP) where mHTT is expressed in neurons, suppression of mHTT aggregation specifically in astrocytes expands the lifespan of HD fly [45]. On the other hand, white matter is degenerated and the oligodendrocyte differentiation is defective in HD [46]. mHTT-expressing microglia are hyperreactive to inflammatory stimuli to cause synaptic dysfunction in dendritic spines [47–49], where neurons try to control microglia activation but fail in HD [50]. Both mHTT and wtHTT are secreted from brain cells [51], where mHTT oligomers disrupt energy metabolism of neighboring cells [52]. mHTT not only affects brain metabolism, it also causes the dysfunction of other organs such as liver [53]. In the below sections, we discuss how mHTT affects astrocytes and oligodendrocytes in the neuropathogenesis of HD.

2.1. Alteration of Astrocyte Function

Astrocytes support neural functions by managing local environments including nutrients, ions, and neurotransmitters. In addition to the role as a generic supporter of neurons, astrocytes are involved in information processing [54], especially in the form of tripartite synapse [55]. Within the tripartite synapse, astrocytes tightly envelop synapses to clear residual neurotransmitters and ions after synaptic activities [56]. Failure in clear-
ance of the residuals leads to accumulation of the neurotransmitters and ions. Excessive buildup of excitatory neurotransmitter such as glutamate is toxic to neurons and eventually causes neurodegenerative diseases [57]. High concentration of extracellular potassium ion depolarizes the membrane potential and contributes to the hyperexcitability of local neurons [58].

In the brain of HD patients, degeneration of medium spiny neurons (MSNs) in the striatum starts in the early stage of the disease before the widespread cell death in the striatum. The mechanism of the degeneration of MSNs is regulated by glutamate-mediated excitotoxicity via N-methyl-D-aspartate receptor (NMDAR) [40]. NMDAR is composed of three types of subunits (GluN1, GluN2A-D, and GluN3A-B), where NMDAR that contains GluN2A or GluN2B control synaptic dynamics [59]. Particularly, GluN2B-type NMDARs are phosphorylated by death-associated protein kinase to serve as toxic receptors [60]. Here, GluN2B-type NMDAR is highly expressed in mature MSNs of striatum, which is the reason behind the selective vulnerability of MSNs in HD [61,62]. Striatal neurons in HD show upregulated surface expression of GluN2B-type NMDAR due to the dysfunction of the huntingtin-interacting protein 14L [63]. Otherwise, gene silencing of a glutamate receptor subunit reverses HD phenotype [64]. Excitotoxicity is also studied systematically. Considering that most glutamatergic input of striatum is from the cortex, destruction of cortico-striatal pathway is a key process in presymptomatic phase of the disease [65]. Dysfunction of MSNs increases the excitation from the cortex in the form of positive feedback loop and exacerbates the excitotoxicity [56]. Interestingly, NMDAR response in the corticostriatal synapse is rescued to normal state by astrocyte-specific reduction of mHTT in BACHD mice [67]. In this context, astrocytes are recently reviewed as a player in excitotoxicity in HD and other neurodegenerative disorders [11,35,39–42,68–77].

In HD astrocytes, mRNA level of excitatory amino acid transporter 2 (EAAT2) is lower compared to that of the normal group [78,79]. In addition, protein level of EAAT2 is reduced throughout whole brain [34,80,81]. Low EAAT2 level is rendered as decreased glutamate uptake [82–84], which results in neuronal degeneration from chronic glutamate stimulation [85]. In addition, downregulation of an inwardly rectifying potassium channel, Kir4.1, in HD astrocytes results in increased extracellular K+ concentration, which subsequently increases the resting membrane potential of nearby neurons to make the neurons more excitable [86]. Interestingly, downregulation of EAAT2 and Kir4.1 in astrocytes not only induces hyperexcitability of neurons, but also induces evoked Ca^{2+} signaling in the astrocytes [87]. Increase of evoked Ca^{2+} level in astrocytes increases sodium pump activity which further increases extracellular K+ concentration [88] (Figure 1, Table 1).

2.2. Alteration of Oligodendrocyte Function

Oligodendrocytes are a type of glial cells in the brain and the spinal cord which produce myelin sheaths and play an important role in maintaining axonal integrity and function. Although oligodendrocytes are less explored in HD in previous studies, defective oligodendrocyte functions and deficient myelination are commonly observed in other neurodegenerative diseases [91]. Myers et al. are the first time to show an increase of oligodendrocytes in the striatum but no changes in astrocytes in postmortem HD brains [92]. Later, the other researchers identify myelin damage and breakdown in pre-symptomatic HD patients [93,94]. The full-length myelin regulatory factor (fMYRF) is self-cleaved to N-terminal myelin regulatory factor (nMYRF) which was transferred from the ER to the nucleus. In HD, binding of mHTT to nMYRF deficits normal bindings of nMYRF transcription factor in nucleus which leads to inhibition of myelination-related genes expression and oligodendrocyte dysfunction [95–97] (Figure 2). On the other hand, Cui et al. show that the expression of proliferator-activated receptor-gamma coactivator (PGC)-1α is significantly downregulated in HD striatal cells and tissues. In HD, mHTT interferes with promoter binding of cAMP response element binding protein (CREB) and TATA-binding protein-associated factor (TAF), which regulate the expression of PGC-1α. This mis-binding leads to the inhibition of PGC-1α expression which may cause reduction of myelin basic
protein (MBP) expression and myelination deficit [98,99] (Figure 2). In parallel with these results, Xiang et al. also show the downregulation of MBP and deficient myelination in the oligodendrocytes of R6/2 transgenic mouse model of HD, and in the striatum of PGC-1α knockout mice as well [100]. Further study is necessary to verify whether PGC-1α rescues myelination in HD models in a cell-type-specific manner.

Figure 1. Dysfunction of cortico-striatal tripartite synapse in HD. mHTT aggregation deregulates transcription of EAAT2 and Kir4.1 in astrocytes. Deregulation of EAAT2 leads to low expression level of astrocyte glutamate transporter and impairment of the glutamate uptake by astrocytes in the tripartite synapse. As a result, excess glutamate in synapse induces hyper-excitability of the post-synaptic neuron (medial spiny neuron in cortico-striatal synapse). Deregulation of Kir4.1 leads to impaired potassium buffering of astrocytes. As a result, elevated potassium ion concentration increases the membrane potential of neurons, where high membrane potential induces hyper-excitability. Prolonged hyper-excitability is rendered as cellular toxicity.

Table 1. Non-cell autonomous cell death pathway in HD related to astrocytes.

| HD Pathology          | Specimen       | Brain Region/Cell Type                  | Experimental Method       | Reference |
|-----------------------|----------------|----------------------------------------|---------------------------|-----------|
| Less EAAT2 mRNA       | Postmortem     | Cingulate cortex                       | RNA sequencing            | [78]      |
|                       |                | Neostriatum                            | In situ hybridization     | [79]      |
| Less EAAT2 protein    | Postmortem     | Striatum                               | Immunohistochemistry      | [34]      |
|                       |                | Striatum, cortex                       | Western blot              | [80]      |
|                       | Mouse; R6/2    | Striatum, cortex, hippocampus, midbrain| Quantitative proteomics   | [81]      |
| Less glutamate uptake | Postmortem     | Prefrontal cortex                      | Glutamate uptake assay    | [84]      |
|                       | Cell; astrocyte| differentiated from Q77 monkey iPSC    | Glutamate uptake assay    | [82]      |
|                       | Mouse; Q175    | Single corticostriatal synapse          | Imaging assay with glutamate sensor | [83]      |
Table 1. Cont.

| HD Pathology | Specimen | Brain Region/Cell Type | Experimental Method | Reference |
|--------------|----------|------------------------|---------------------|-----------|
| Less Kir4.1 mRNA | Postmortem cingulate cortex | RNA sequencing | [78] |
| Less Kir4.1 protein Higher extracellular K⁺ More excitable | Mouse; R6/2 Striatal MSN and astrocyte | qPCR, IHC, Western blot, Virus microinjection, Electrophysiology | [86] |
| Altered Ca²⁺ signal | Mouse; R6/2 Striatal astrocyte | Virus microinjection Electrophysiology | [87] |
| More excitotoxicity | Cell; neuron and astrocyte | Co-culture of HD neurons and astrocytes from human iPSC | Cell count after glutamate exposure | [89] |

---

**Figure 2.** Oligodendrocyte dysfunction in HD. In the first pathway, full-length MYRF is self-cleaved to nMYRF which detaches from ER and is translocated to the nucleus to regulate the expression of myelin related genes. In HD, N-terminal mHTT binds nMYRF causing abnormal binding of nMYRF and deficit myelin genes expression. Second pathway shows inhibition of PGC-1α expression by interference of mHTT in co-binding of CREB and TAF4, leading to reduced activity in the cholesterol biosynthesis pathway and myelination deficit. Created with BioRender.com.

**3. The Role of Epigenetic Modifications and Noncoding RNAs in the Pathogenesis of HD**

Better understanding of epigenetic mechanisms may provide important insights, resulting in improved therapeutic approaches for treating HD [101]. In this section, we discuss the epigenetic changes and mechanisms that are associated with the pathogenesis of HD. We focus on two main epigenetic alterations that influence chromatin structure: DNA and histone modifications [102]. DNA methylation and hydroxymethylation have
been involved in different neurodevelopmental and psychiatric disorders [103–105]. In DNA methylation, methyl groups are transferred to the cysteine 5 position of cytosine via the action of DNA methyltransferases [106]. Ng et al. propose that mHTT has a significant effect on changing the methylation of promoter regions of octamer-binding transcription factor 1 (OCT4), sex determining region Y-box 2 (SOX2), and Nanog homeobox (NANOG) as these genes are involved in neurogenesis. Therefore, inhibition of the expression level of these genes may lead to neurogenesis impairment and cognitive decline in HD [107] (Figure 3). In addition, histone modification is another major epigenetic mechanism which plays a special role in unraveling the pathogenesis of HD. CREB binding protein (CBP) interacts with several transcription factors such as specificity protein 1 (SP1), TAF, and RNA polymerase II, and acts as a co-activator or a repressor of transcription [108,109]. The CBP can also be considered as a histone acetyltransferase which acetylates histones to alter chromatin structure [110]. The mHTT interaction with CBP blocks its transcriptional co-activator function and inherent CBP histone acetyltransferase activity [111]. Therefore, CBP sequestration and depletion are accompanied by histone hypoacetylation, resulting in neuronal transcriptional dysfunction and neurotoxicity [112–114] (Figure 3).

Our group has found that SET domain bifurcated histone lysine methyltransferase 1 (SETDB1/ESET), a histone H3 at lysine 9 (H3K9)-specific methyltransferase, is elevated in the striatal neurons of HD patients and HD transgenic (R6/2) mice [115]. In parallel, the level of histone H3K9me3 is increased in the striatal neurons of HD patients and in HD transgenic (R6/2) mice. This study has proven that the SETDB1-H3K9me3 pathway is involved in silencing of genes in HD. Interestingly, not only SETDB1 modulates the nuclear gene transcription though heterochromatin remodeling, but it also down regulates

![Figure 3. Epigenetic modifications associated with HD. The promoter regions of neurogenesis-related genes, OCT4, SOX2, and NANOG, are methylated in cells expressing mHTT which can lead to impaired neurogenesis. On the other hand, mHTT sequestres CBP in nuclear inclusions which causes the hypermethylation and hypoacetylation of histone proteins and CBP depletion. Depletion of CBP from the nucleus of cells leads to histone hypoacetylation, nuclear and nucleolar transcriptional dysfunction and increase in neurotoxicity. Created with BioRender.com.](image-url)
the nucleolar gene transcription (ribosomal DNA components) by increasing methylation of upstream binding protein 1 (UBF1). SETDB1 interacts with UBF1 and trimethylates at lysine 232/235 in the nucleolus of striatal cells. As a result, trimethylated UBF1 leads to nucleolar chromatin condensation and downregulates the transcription of ribosomal DNA (rDNA) [12]. This study presents a novel epigenetic mechanism that SETDB1-UBF1 trimethylation pathway is associated with nucleolar chromatin remodeling and dysfunction of rDNA transcription in the pathogenesis of HD.

Moreover, several studies have focused on microRNAs (miRNAs) which are involved in the early differentiation, development, and function of neurons [116,117]. miR-146a is one of the major regulators of the NF-κB pathway which can also target human and mouse HTT gene [118,119]. Das et al. demonstrate that heat shock factor 1 is regulated by this miRNA, resulting suppression of mHTT aggregates in HD cells [120]. Another study confirmed that miR-214 directly targets the HTT gene which can suppress mHTT aggregation in an HD mouse striatal cell and HEK293T cell [120,121]. On the other hand, Bucha et al. showed the upregulation of miRNA-214 in HD cells could regulate mitofusin2, resulting in alteration of mitochondrial morphology [122]. Therefore, this miRNA can be considered as a critical node for therapeutic targets in HD pathogenesis.

4. Roles of Wild Type HTT (wtHTT) Versus mHTT in Vesicle Trafficking

Understanding the exact molecular and cellular functions of wtHTT and mHTT is crucial in further clarifying the pathogenesis of HD. wtHTT is involved in axonal transport, which is essential for neuronal synaptic activity [123]. Transport of cargo is important for neuron to work properly because of its unique morphology containing axons and dendrites. Vesicular transport is accelerated by overexpression of wtHTT [124]. There are emerging models to explain how wtHTT coordinates vesicular transport and ongoing studies to discover a more detailed mechanism of coordination and the HD pathology related to vesicle transport [125] (Figure 4).

![Figure 4](image-url)

**Figure 4.** Role of HTT in normal vesicular transport and role of mHTT in disturbed vesicular transport in HD. In normal conditions, HTT participates in motor protein complex with dynactin, dynein, and kinesin. In addition, HTT recruits GAPDH to vesicles to supply energy, ATP to motor proteins. In HD, polyglutamine expansions of the mHTT sequester GAPDH and motor proteins. Microtubules are acetylated by mHTT to hinder binding of motor proteins on the microtubules.

wtHTT recruits glyceraldehyde-3-phosphate dehydrogenase (GAPDH) to transport vesicles, whereas vesicular GAPDH produce adenosine 5′-triphosphate (ATP) to provide energy for the transport [126]. In HD pathogenesis, GAPDH is sequestered by mHTT [127,128], where the sequestration of GAPDH is rescued by high-affinity RNA aptamers that specifically recognize mHTT [129]. In addition, HTT forms complexes of motor proteins with huntingtin-associated protein-1 and p150Glued subunit of dynactin [130]. HTT-associated protein-1 binds to both kinesin-1 and vesicles to serve as an adaptor [131]. Huntingtin’s recruitment of kinesin-1 is governed by the phosphorylation of wtHTT at serine421 (Ser421), which stimulates anterograde transport [132]. Interestingly, phosphorylation of HTT (Ser421) protects against the mHTT toxicity, where the endogenous level of phosphorylated HTT (Ser421) is least in the striatum [133].
Defects in the axonal transport are associated with neurodegenerative diseases. For example, mutations in amyloid beta precursor protein obstruct motor protein activity of the hippocampal and cortical neurons in AD, and mutation in superoxide dismutase type-1 impede binding of motor proteins to neurofilaments of motor neurons in ALS [134]. In fact, fast axonal transport is commonly disrupted in polyglutamine-expansion diseases [135]. In HD, fast axonal transport is slowed down specifically in striatal neurons [136]. The impairment of the vesicular transport induces axonal degeneration, which is the early neuropathology of HD [137].

Pathogenic HTT disrupts the motility of vesicle complex, accessory proteins, and molecular motors [138], hence, the efficiency of vesicle trafficking [131,139] (Figure 4). Comparably, both HTT-depleted neurons and mHTT-expressing neurons suffer from defective axonal transport [140], where motor proteins are sequestered by mHTT [141]. Tubulin acetylation is also reduced in HD resulting in reduced binding of motor proteins to microtubules [142]. Vesicle trafficking related proteins such as HTT interacting protein 1, dynamin, and endophilin-A3 are depleted by mHTT bodies [143].

On the other hand, mHTT activates axonal c-Jun amino-terminal kinase3 via stress-signaling kinase [144], where inhibition of the c-Jun amino-terminal kinase/c-Jun partially restores striatal neurodegeneration in HD [85]. Consequently, kinesin-1 is phosphorylated at serine 176, which results in detachment of kinesin-1 and cargo from the microtubules [145].

Despite the growing evidence of mHTT and its effects on vesicle trafficking in neurons, further study is necessary to define why MSNs are much more susceptible to mHTT than other neuronal cell types. Additionally, precise cellular and molecular mechanism of mHTT oligomers versus mHTT aggregates-dependent vesicle trafficking should be determined.

In addition, wtHTT is also involved in autophagy as reviewed in [146]. wtHTT form complex with sequestosome 1 to enhance cargo recognition, where depletion of wtHTT results in empty autophagosome [147]. C-terminal domain of wtHTT has structural homology with yeast autophagy scaffold protein 11 and both proteins show similar protein–protein interaction patterns [148]. Interestingly, deletion of N-terminal domain of wtHTT in mouse suffers from DNA damage in striatum and cortex without any difference in autophagy function [149]. wtHTT is also associated with ER, where ER stress release the wtHTT to promote autophagy (reviewed in [150]). In addition, wtHTT has important role in homeostasis of presynaptic and postsynaptic terminal [151]. Loss of wtHTT lead to dysfunction of synaptic vesicle endocytosis in striatal neurons [152].

We need to provide attention to an important HD pathophysiology that the dysfunctions of central nervous system and other organs in HD are caused by mHTT accumulation as well as by the loss of functionality of wtHTT protein. Molecular simulation reveals that mHTT oligomer also sequester wtHTT [153]. Indeed, wtHTT protein expression level is inversely correlated to the age of onset [154]. In macrophage, reduced wtHTT level is associated with decreased cytokine and increased phagocytosis [155]. Research is ongoing to reveal the wtHTT function and structure further. RNA-seq of wtHTT knockout neural cell shows that wtHTT has a role in development of neurons and neurotransmission [156]. Cryo-electron microscopy structure of wtHTT confirms its role in protein–protein interaction [157]. The importance of the loss of functionality of wtHTT is associated with clinical safety of HTT gene therapy as reviewed previously [158].

5. Mitochondria Dysfunction in HD

A growing body of evidence show that mitochondrial dysfunctions, including membrane potential and respiratory function deficits, Ca\(^{2+}\) buffering capacity reduction, and mitochondrial number and morphology alteration, play a critical role in HD pathogenesis [159–165]. The mHTT aggregation reduces the mitochondrial membrane potential and increases the level of mitochondrial matrix Ca\(^{2+}\) loading that leads to decreased ATP level and enhanced reactive oxygen species (ROS) [160,166,167]. Moreover, the release of cytochrome c from dysfunctional mitochondria leads to activation of caspases 9 and 3 which are involved in apoptosis, resulting in neuronal cell death [168,169] (Figure 5). On
the other hand, Yablonska et al. show mHTT binding with high affinity to translocase of mitochondrial inner membrane 23 (TIM23) complex in mitochondrial intermembrane space leads to inhibition of import of nuclear-encoded proteins through TIM23 [14]. Therefore, the mHTT–TIM23 complex interaction alters mitochondrial proteome, resulting in mitochondrial dysfunction in HD [170] (Figure 5). In addition, Guo et al. showed that valosin-containing protein (VCP) is bound to mHTT as a binding protein on the mitochondria. Mitochondria-accumulated VCP works as a mitophagy adaptor to bind to the autophagosome component, microtubule-associated proteins 1A/1B light chain 3B (LC3), leading to enhanced mitophagy, reduced mitochondrial mass, and ultimately, neuronal cell death [28,171] (Figure 5). Moreover, the previous studies demonstrated that down regulation of wtHTT is related to mitochondria dysfunction by inability of the mitochondria to generate ATP [172] and diminished purines and inosine monophosphate [6].

Figure 5. Mitochondria dysfunction associated with HD. mHTT aggregation disrupts the mitochondrial membrane potential and increases excitotoxin-induced Ca2+ influx which leads to decreased ATP generation and increased ROS. Mitochondria dysfunction results in release of cytochrome C from the mitochondria which triggers the activation of apoptotic cascade via caspases 9 and 3, and neuronal injury. On the other hand, in HD, mHTT binds with high-affinity to TIM23 in mitochondrial intermembrane space, causing diminished levels of nuclear-encoded proteins imported through TIM23 and subsequently, neuronal death. Finally, VCP is selectively translocated to the mitochondria, where it is bound to mHTT and LC3 to enhance mitophagosome production, and reduce mitochondrial mass and energy supply, causing neuronal cell death. Created with BioRender.com.

6. Therapeutic Approaches for Huntington’s Disease

Despite remarkable efforts to overcome the symptoms of HD, effective therapeutic targets are still very limited in HD. Furthermore, no standard treatment has been established for HD. HD transgenic mouse models have been used for translational study with many candidate drugs before conducting clinical trials with patients, but the efficacy of most drugs is lower than expected [173]. Accordingly, the benefits of translating the therapeutic efficacy from the HD transgenic mouse models to human patients are not clear.

Gene editing method and strategy have been attempted for treating various genetic disorders including HD. Clustered regularly interspaced short palindromic repeats and (CRISPR) and CRISPR-associated genes (CRISPR/Cas9) has been applied haplotype-specifically to common promoter-local single-nucleotide polymorphisms (SNPs) for the
selective deletion of mHTT [174–177]. Otherwise, Zinc finger proteins containing the Kruppel associated box (KRAB-ZFPs), short hairpin RNA (shRNA), small interfering RNA (siRNA), and miRNA have been examined to impair transcription of mHTT [178–185]. To use siRNA or antisense oligonucleotide to knock-down mRNA of mutant Hunting requires repetitive administration. shRNA treatment lasts relatively longer than siRNA treatment; however, the dosage control of shRNA treatment is limited [186]. miRNA therapy suffers from off-target effect in general, which is recently overcome using in silico analysis [187]. Glutamine repeat-binding [188] and deletion [189] on mHTT gene are also effective in HTT lowering and alleviate HD phenotypes. For further information, gene targeting approaches are reviewed in [190–201].

Among many small compounds, epigenetic modulators have been used for rescuing transcriptional dysfunction in HD. For example, phenylbutyrate, sodium butyrate, histone deacetylases inhibitor (HDACi) 4b and LBH589, Tubastatin A, and CKD-504 hinder histone deacetylase increase the acetylation of H3K9, and improve neuropathology, behaviors, and survival of HD transgenic mice [202–208]. Importantly, epigenetic compounds exhibit transgenerational effect in HD animal models [205]. Mithramycin, a DNA binding drug, inhibits expression of histone methyltransferase, reduces H3K9me3 level and heterochromatin condensation, and ameliorates symptoms of HD [209]. In order to improve the efficacy of epigenetic compounds, further efforts to reduce the side effect of these drugs need to be made.

In addition to HD genetic and epigenetic targets, pathologic phenotypes including HTT fragmentation and aggregates, transcriptional dysfunction, oxidative stress, apoptosis, autophagy dysfunction, and excitotoxicity appear to be reasonable drug targets [101] (Table 2). The most effective therapeutic strategy in HD is to target the inhibition of aggregation or fragmentation of mHTT, because mHTT is directly responsible for the pathogenesis of HD. Cystamine, Congo red, Chrysamine G, direct fast yellow, and trehalose are drugs that bind to polyglutamine or block oligomerization, and consequently inhibit the aggregation of mHTT. Congo red, an organic compound and diazo dye, binds to β-sheets of protein structure of mHTT and prevents polyglutamate oligomerization. Since Congo red cannot cross the blood–brain barrier, compounds with similar structure of Congo red are discovered as potential drugs. Chrysamine G and direct fast yellow are found to effectively inhibit mHTT aggregation [210]. Saccharides including trehalose also bind directly to the polyglutamate region of mHTT to suppress the mHTT aggregation effectively [211]. Both antibodies which binds polyproline domain of mHTT and Dnaj heat shock protein family member B6 also reduce mHTT aggregation [212]. Otherwise, insulin, exendin-4, GM1, RCAN1-IL, and SGK block mHTT aggregation by increasing mHTT phosphorylation and modifying mHTT toxicity through post-translational modification. Increasing the phosphorylation of mHTT enhances solubility and decreases aggregation. Surprisingly, phosphorylation of mHTT on Ser 421 is known to be neuroprotective [213,214]. Formation of mHTT aggregate is exacerbated by transglutaminase, which cross-links mHTT. Inhibition of transglutaminase with cystamine reduces abnormal behavior, extends lifespan, and prevents weight loss of HD transgenic (R6/2) mice. In addition, cystamine injected HD mice have higher expression level of Dnajb1, which catalyze ATP hydrolysis. In addition to the mHTT aggregation, fragmentation of mHTT has been a plausible therapeutic target for HD because the pathology of HD is exacerbated by mHTT fragments including polyglutamate region [215]. Minocycline and Z-VAD-FMK inhibit caspases to prevent the proteolysis of mHTT and improve neuropathology of HD transgenic mice [216].

Interestingly, Rieux et al. (2020) tested whether a parabiosis therapy, an in vivo blood transfusion via surgical linking of two bodies, can reduce mHTT propagation and pathology in HD transgenic mice (zQ175 mice) [217]. It is concluded that blood transfusion improves mitochondrial activity in peripheral organs and ameliorates neuropathology in MSNs of striatum. This study indicates that healthy blood can diminish the pathogenicity of circulating mHTT. If the concentration of mHTT exceeds a certain concentration in the body, it is likely to cause a disease onset of HD systemically. In this paradigm, reducing
the concentration of mHTT by removing circulating mHTT with blood transfusion can be another treatment. However, application of the parabiosis therapy for HD may need further verification in regard to unexpected adaptive immune reactions in vivo.

Mitochondrial dysfunction is also one of the therapeutic targets in HD. Creatine is applied to restore mitochondrial dysfunction as it deactivates mitochondrial permeability transition [218]. Coenzyme Q10 promotes electron transport chain activity, which in turn improves mitochondrial respiration [218–220]. Both creatine and coenzyme Q10 have been used as beneficial compounds in HD and progressed up to Phase II clinical trials. Mitochondrial dysfunction induces oxidative stress, which can be managed by antioxidants (reviewed in [221]). PGC-1α is associated with transcriptional regulation of mitochondria-related genes and is also the target of HD therapy (reviewed in [222]). rhIGF-1 increases glucose uptake and regulates energy metabolism in striatal neurons, and its therapeutic effect has been tested in HD transgenic mouse models (R6/2 and YAC128) [223]. Autophagy is also involved in the clearing and recycling of mHTT in MSNs and its function is impaired in HD [224]. Niclosamide reduces mHTT by increasing autophagy activity [225]. It seems likely that niclosamide is therapeutically more effective in increasing lysosomal degradation of ubiquitinated molecules including ubiquitinated mHTT rather than activating proteasomal activity [226]. Apoptotic cell death of MSNs has been a therapeutic target in HD [227]. MAP4343, 17EE2, and isoquercitrin are known to control stress responses and reduce apoptosis of MSNs in HD [228]. Z-VAD-FMK, Z-DEVD-FMK, Z-LEHD-FMK, FG3d, and lithium chloride are well-known apoptosis inhibitors and used to treat HD animal models (C. elegans and Rat) [216,226,227,229,230]. Laquinimod increase the brain-derived neurotrophic factor level in striatum of R6/2 mouse model and has the neuroprotective effect [231].

Continuous stimulation by excitatory or inhibitory neurotransmitter can damage MSNs in HD. Notably, controlling glutamate-induced neurotoxicity is one of many therapeutic strategies for treating HD and other neurodegenerative disorders (reviewed in [232]). Silencing of a glutamate receptor subunit could reverse HD phenotype [64]. Activation of NMDA receptors and cation channels elevates intracellular Ca\(^{2+}\) flux, impairs mitochondria function, and triggers neuronal cell death pathways. Memantine acts as an inhibitor of NMDA receptor, draws attention in HD therapy, and its clinical trials are on-going at phase 2 and phase 4, respectively. Otherwise, necrostatin-1, an inhibitor of receptor-interacting serine/threonine-protein kinase 1 (RIPK1) and necrosis, shows positive effects for delaying the onset and improving motor behaviors while the survival extension is not improved in HD transgenic (R6/2) mice [77,233,234].

| Target | Strategy | Mode of Action | Disease Model | Clinical Trial & NCTno. | References |
|--------|----------|----------------|---------------|-------------------------|------------|
| mHTT gene | CRISPR/Cas9 | Excise mHTT DNA selectively | Cell iPS, Mouse BacHD, Mouse HD140Q, Mouse R6/2 | | [174] |
| shRNA | Inhibition of translation or transcriptdegradation | Mouse R6/1.2, Mouse R6/2, Mouse N171-82Q, Mouse HTT injected, Mouse Hdh-150Q | | | [178,179] |
| siRNA | | | | | [180] |
| miRNA | | | | | [181] |
| | | | | | [182] |
| | | | | | [183] |
| | | | | | [184] |
| | | | | | [185] |
| Antisense nucleotide | | | | | [235] |
| | | | | | NCT04120493 |
| | | | | | [185] |
| | | | | | [236,237] |

Table 2. Therapeutic targets for HD.
Table 2. Cont.

| Target                     | Strategy                  | Mode of Action                        | Disease Model          | Clinical Trial & NCTno.                  | References |
|----------------------------|---------------------------|---------------------------------------|------------------------|------------------------------------------|------------|
| Transcriptional dysregulation | Phenylbutyrate            | Inactivate histone deacetylase        | Mouse N171-82Q         | Phase II, NCT00212316                   | [202]      |
|                            | Sodium butyrate           |                                       | Mouse R6/2             |                                          |            |
|                            | HDACi 4b                  |                                       | Mouse N171-82Q         |                                          | [203]      |
|                            | HDACi LBH589              |                                       | Transgenic Rodent HD   |                                          | [204–206]  |
|                            | Tubastatin A              |                                       | Cell primary neuron    |                                          | [207]      |
|                            | CKD-504                   |                                       |                        | Phase I, NCT03713892                    | [208]      |
| mHTT aggregation           | Mithramycin               | Increase H3K9                         | Mouse R6/2             |                                          | [209]      |
|                            | Cystamine                 | Suppress mHTT crosslinking            | Mouse R6/2             |                                          | [238,239]  |
|                            | Congo red, ChrysamineG, Direct fast yellow Trehalose | Bind and inhibit polyglutamine-oligomerization | Mouse R6/2 | | [240]      |
| mHTT fragmentation         | Minocycline               | Inhibit caspase                        | Mouse R6/2             | Phase III, NCT00277355                  | [241]      |
|                            | Z-VDAD-FMK                | Cell X57                              | Cell primary neuron    |                                          | [241]      |
| mHTT lowering              | Blood transfusion         | Remove circulating mHTT               | Mouse zQ175            |                                          | [217]      |
| mHTT post-modification     | Insulin, exendin-4 GM1    | Increase mHTT phosphorylation         | Cell SH-SY5Y           |                                          | [242]      |
|                            | RCAN1-1L                  |                                       | Mouse YAC128           |                                          | [243]      |
|                            | S GK                      |                                       | Cell ST4A              |                                          | [244]      |
|                            | Insulin, exendin-4 GM1    |                                       | Cell primary neuron    |                                          | [245]      |
|                            | RCAN1-1L                  |                                       |                        |                                          |            |
|                            | S GK                      |                                       |                        |                                          |            |
| Transactivation            | KD3010                    | Increased PPARδ transactivation       | Mouse pCAGGS-loxP-STOP-loxP | [246]                                    |            |
| Mitochondrial dysfunction  | Creatine                  | Inactivate mitochondrial permeability transition | Mouse R6/2 | Phase II, NCT00026988                  | [218]      |
|                            | Coenzyme Q10              | Enhance electron transport            | Mouse YAC128           | Phase II, NCT00277355                  | [219,220]  |
|                            | PGC-1α                    | Upregulate mitochondrial gene         | Mouse R6/2             |                                          | [222]      |
| Metabolism                 | rhIGF-1                   | increase glucose uptake               | Mouse YAC128           |                                          | [223]      |
|                            | Niclosamide               | Inhibit mTOR                           | Cell HEK293, N2a       |                                          | [225]      |
| Autophagy                  | MAP4343, 17βE2, Isoquercitrin | Regulate stress response              | C. elegans HD mutants |                                          | [228]      |
| Apoptosis                  | Z-VDAD-FMK, Z-DEVAD-FMK, Z-LEHD-FMK, PG3d Lithium chloride | Inhibit caspase | Cell primary neuron | | [227] |
|                            | Memantine                 | Inhibit NMDA receptor                  | Phases II, III, NCT00652457 | [229] | [230] |
|                            | Necrostatin-1             | Inhibit RIP1 kinase                    | Mouse R6/2             |                                          | [233,247]  |

7. Conclusions

Since the mutation of HTT gene at exon 1 with glutamine repeats was identified as the cause of HD in 1993 [2], many studies have shown that mHTT proteins directly cause the neuropathogenesis of HD. wtHTT plays an important role in vesicular transport,
which is an essential cellular event in MSNs, whereas mHTT disrupts vesicle transport by sequestering motor proteins. Understanding of exact mechanisms on the mHTT-induced selective neuronal damage in the neostriatum is pivotal to develop beneficial therapeutic targets or strategies to ameliorate the neurodegeneration in HD. In this context, further investigations about effective clearance or detoxification of mHTT remain to be performed.

The brain is a multicellular organ. Accordingly, it is possible that mHTT-induced cellular dysfunctions are varied and differentially modulated in specific brain regions and cell-type specific manner. In terms of autonomous versus non-cell autonomous neuronal damage, it is also critical to determine which brain cell-types (e.g., excitatory neurons, inhibitory neurons, astrocytes, and oligodendrocytes) are vulnerable to mHTT and contribute to the pathogenesis of HD [11,70]. Importantly, gliosis, production of new astrocytes, microglia, and oligodendrocytes, is a prominent pathology in HD as well as in other neurodegenerative disorders (reviewed in [74,77]). Therefore, it is necessary to define how mHTT affects the fate of neuron and glia, and whether therapeutic targets can selectively modulate and rescue cell-type specific functions in HD.

The scope of this review is to briefly introduce the previous and recent studies about mechanisms of HD pathologies and therapeutic strategies and that our review has limitation in the scope. Just in case, for the readers need further information, we recommend the previous reviews dealt with the specific aspects of striatal vulnerability [248], white matter phenotype [249], cerebellar dysfunction [250], progression of cell type-specific phenotype [251], microglial activation [252], synapse [253], intracellular transmission of mHTT [254], protein–protein interactions [255], biochemical alterations and HTT dynamics [256,257], posttranslational modifications [258], proteostasis [259], autophagy [260,261], redox homeostasis [262], metabolism [263,264], HTT mRNA [265,266], Ca\(^{2+}\) and dopamine signaling [61], inflammation [267], in vitro modelling of HD [268,269], striatal neurogenesis [270], stem cell treatment [271–279], electric stimulation therapy [280], network connectivity in presymptomatic HD brain [281], non-motor symptoms [282], gut microbiome [283], human immunodeficiency virus [284], diagnosis [285,286], clinical progression [287], treatment for the symptoms [288], physical therapy [289], psychological interventions [290,291], and management of agitation [292]. Collectively, the previous studies have potential to reveal spatiotemporal and cell-type specific mechanism of HD pathology. The future challenges in HD research are brought by the complexity of the pathology from biochemical level [293–303] to system level [304–308]. Accordingly, the ultimate mechanisms of HD pathology can be further scrutinized by state-of-the-art research methods such as multi-omics approach combining transcriptome, proteome, and interactome [309], big data analysis with machine learning [310], and meta-analysis combining the publicly available data [311]. On the other hand, the potential HD therapeutics should specifically modulate the function of the striatal neurons while they prevent the adverse behavior of glial cells. High-throughput in silico and in vitro screening of chemical libraries [312–316] are expected to expedite the designing of beneficial compounds for HD.

Previous studies indicate that epigenetic cellular events have been emerged as potential therapeutic targets in HD [12,109]. The reversible characters of epigenetic modifications during the pathogenesis of HD are reasonable therapeutic targets. It is highly expected that we can prevent neuronal damage more efficiently by balancing the epigenetic disequilibrium in HD before the pathogenesis becomes irreversible and degenerative under HD stress condition. In this regard, future therapeutic strategies and agents to treat HD should consider appropriate epigenetic targets and cell-type specificity. On the other hand, identification of blood cell-derived epigenetic markers that can mimic the brain molecular pathology, will facilitate the advanced diagnosis and treatment of HD. Taken together, development of cell-type specific epigenetic therapeutic targets will pave a way to slow down the onset and progress of HD.
**References**

1. Exuzides, A.; Crowell, V.; Reddy, S.R.; Chang, E.; Yohrling, G. Epidemiology of Huntington’s disease (HD) in the US medicare population. *Neurology* **2020**, *94*, 670.

2. The Huntington’s disease collaborative research group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington’s disease chromosomes. *Cell* **1993**, *72*, 971–983. [CrossRef]

3. Di Prospero, N.A.; Fischbeck, K.H. Therapeutics development for triplet repeat expansion diseases. *Nat. Rev. Genet.* **2005**, *6*, 756–766. [CrossRef] [PubMed]

4. Ross, C.A. Polyglutamine pathogenesis: Emergence of unifying mechanisms for Huntington’s disease and related disorders. *Neuron* **2002**, *35*, 819–822. [CrossRef]

5. Cattaneo, E.; Rigamonti, D.; Goffredo, D.; Zuccato, C.; Squitieri, F.; Sipione, S. Loss of normal huntingtin function: New developments in Huntington’s disease research. *Trends Neurosci.* **2001**, *24*, 182–188. [CrossRef]

6. Tomczyk, M.; Glaser, T.; Ulrich, H.; Slominska, E.M.; Smolenski, R.T. Huntingtin protein maintains balanced energetics in mouse cardiomyocytes. *Nucleosides Nucleotides Nucleic Acids* **2020**, accepted. [CrossRef]

7. Rüb, U.; Seidel, K.; Heinsen, H.; Vonsattel, J.P.; den Dunnen, W.F.; Korf, H.W. Huntington’s disease (HD): The neuropathology of skeletal muscle but not heart of late-stage R6/2 mice. *Brain Pathol.* **2019**, *29*, 726–740. [CrossRef] [PubMed]

8. DiFiglia, M.; Sapp, E.; Chase, K.O.; Davies, S.W.; Bates, G.P.; Vonsattel, J.P.; Aronin, N. Aggregation of Huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. *Science* **1997**, *277*, 1990–1993. [CrossRef] [PubMed]

9. Ross, C.A. Intranuclear neuronal inclusions: A common pathogenic mechanism for glutamine-repeat neurodegenerative diseases? *Neuron* **1997**, *19*, 1147–1150. [CrossRef]

10. Kojer, K.; Hering, T.; Bazenet, C.; Weiss, A.; Herrmann, F.; Taanman, J.-W.; Orth, M. Huntingtonin aggregates and mitochondrial pathology in skeletal muscle but not heart of late-stage R6/2 mice. *J. Huntingt. Dis.* **2019**, *8*, 145–159. [CrossRef] [PubMed]

11. Creus-Muncunill, J.; Ehrlich, M.E. Cell-autonomous and non-cell-autonomous pathogenic mechanisms in Huntington’s disease: Insights from in vitro and in vivo models. *Neurotherapeutics* **2019**, *16*, 957–978. [CrossRef]

12. Lee, J.; Hwang, Y.J.; Kim, K.Y.; Kowall, N.W.; Ryu, H. Epigenetic mechanisms of neurodegeneration in Huntington’s disease. *Neurotherapeutics* **2013**, *10*, 664–676. [CrossRef] [PubMed]

13. Trushina, E.; Dyer, R.B.; Badger, J.D.; Ure, D.; Eide, L.; Tran, D.D.; Vrieze, B.T.; Legendre-Guillemin, V.; McPherson, P.S.; Mandavilli, B.S. Mutant huntingtin impairs axonal trafficking in mammalian neurons in vivo and in vitro. *Mol. Cell. Biol.* **2004**, *24*, 8195–8209. [CrossRef] [PubMed]

14. Yablonowska, S.; Ganesan, V.; Ferrando, L.M.; Kim, J.; Pyzel, A.; Baranova, O.V.; Khattar, N.K.; Larkin, T.M.; Baranov, S.V.; Chen, N.; et al. Mutant huntingtin disrupts mitochondrial proteostasis by interacting with TIM23. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 16593–16602. [CrossRef] [PubMed]

15. Yamanishi, E.; Hasegawa, K.; Fujita, K.; Ichinose, S.; Yagishita, S.; Murata, M.; Tagawa, K.; Akashi, T.; Eishi, Y.; Okazawa, H. A novel form of necrosis, TRIAD, occurs in human Huntington’s disease. *Acta Neuropathol. Commun.* **2017**, *5*, 19. [CrossRef] [PubMed]

16. Lin, C.-L.; Wang, S.-E.; Hsu, C.-H.; Sheu, S.-J.; Wu, C.-H. Oral treatment with herbal formula B307 alleviates cardiac failure in aging R6/2 mice with Huntington’s disease via suppressing oxidative stress, inflammation, and apoptosis. *Clin. Interv. Aging* **2015**, *10*, 1173–1187. [PubMed]

17. Bassi, S.; Tripathi, T.; Monziani, A.; Di Leva, F.; Biagioli, M. Epigenetics of Huntington’s disease. *Adv. Exp. Med. Biol.* **2017**, *978*, 277–299. [PubMed]

18. Valor, L.M. Understanding histone deacetylation in Huntington’s disease. *Oncotarget* **2017**, *8*, 5660–5661. [CrossRef] [PubMed]

19. Li, S.H.; Li, X.J. Huntingtonin-protein interactions and the pathogenesis of Huntington’s disease. *Trends Genet.* **2004**, *20*, 146–154. [CrossRef] [PubMed]

20. Riley, B.E.; Orr, H.T. Polyglutamine neurodegenerative diseases and regulation of transcription: Assembling the puzzle. *Genes Dev.* **2006**, *20*, 2183–2192. [CrossRef] [PubMed]

21. Yamanaka, T.; Miyazaki, H.; Oyama, F.; Kurosawa, M.; Washizu, C.; Doi, H.; Nukina, N. Mutant Huntingtin reduces HSP70 expression through the sequestration of NF-Y transcription factor. *Ennio. J.* **2008**, *27*, 827–839. [CrossRef] [PubMed]
49. O’Regan, G.C.; Farag, S.H.; Casey, C.S.; Wood-Kaczmar, A.; Pocock, J.M.; Tabrizi, S.J.; Andre, R. Human Huntington’s disease pluripotent stem cell-derived microglia develop normally but are abnormally hyper-reactive and release elevated levels of reactive oxygen species. *J. Neuroinflammation* **2021**, *18*, 94. [CrossRef]

50. Bolla, A.C.; Valente, T.; Miguez, A.; Brito, V.; Gines, S.; Solà, C.; Straccia, M.; Canals, J.M. CD200 is up-regulated in R6/1 transgenic mouse model of Huntington’s disease. *PLoS ONE* **2019**, *14*, e0224901.

51. Caron, N.S.; Banos, R.; Yanick, C.; Aly, A.E.; Byrne, L.M.; Smith, E.D.; Xie, Y.; Smith, S.E.; Pothuri, N.; Black, H.F.; et al. Mutant huntingtin is cleared from the brain via active mechanisms in Huntington disease. *J. Neurosci.* **2021**, *41*, 780–796. [CrossRef] [PubMed]

52. Sameni, S.; Zhang, R.; Digman, M.A. The phasor FLIM method reveals a link between a change in energy metabolism and mHtt protein spread in healthy Mammalian cells when co-cultured with Huntington disease cells. *Methods Appl. Fluoresc.* **2021**, 9, 015005. [CrossRef]

53. Singh, A.; Agrawal, N. Deciphering the key mechanisms leading to alteration of lipid metabolism in Drosophila model of Huntington’s disease. *Biochim. Et. Biophys. Acta (BBA)-Mol. Basis Dis.* **2021**, *1867*, 166127. [CrossRef] [PubMed]

54. Sancho, L.; Contreras, M.; Allen, N.J. Glia as sculptors of synaptic plasticity. *Neurosci. Res.* **2020**, **167**, 17–29. [CrossRef]

55. Brymer, K.J.; Barnes, J.R.; Parsons, M.P. Entering a new era of quantifying glutamate clearance in health and disease. *Front. Cell. Neurosci.* **2020**, *14*, 348. [CrossRef] [PubMed]

56. Schmidt, M.E.; Caron, N.S.; Aly, A.E.; Lemarié, N.; Black, H.F.; et al. RNA-seq identifies Huntington disease astrocyte states. *Acta Neuropathol. Commun.* **2019**, *7*, 1175. [CrossRef]

57. Ehrlich, M.E. Huntington’s disease and the striatal medium spiny neuron: Cell-autonomous and non-cell-autonomous mechanisms. *Front. Neurosci.* **2020**, *14*, 82. [CrossRef]

58. Bolla, A.C.; Valente, T.; Miguez, A.; Brito, V.; Gines, S.; Solà, C.; Straccia, M.; Canals, J.M. CD200 is up-regulated in R6/1 transgenic mouse model of Huntington’s disease. *PLoS ONE* **2019**, *14*, e0224901.

59. Caron, N.S.; Banos, R.; Yanick, C.; Aly, A.E.; Byrne, L.M.; Smith, E.D.; Xie, Y.; Smith, S.E.; Pothuri, N.; Black, H.F.; et al. Mutant huntingtin is cleared from the brain via active mechanisms in Huntington disease. *J. Neurosci.* **2021**, *41*, 780–796. [CrossRef] [PubMed]

60. Miller, B.R.; Bezprozvanny, I. Corticostriatal circuit dysfunction in Huntington’s disease: Intersection of glutamate, dopamine and calcium. *Future Neuro.** 2010**, *5*, 735–756. [CrossRef]

61. Raymond, L.A.; André, V.M.; Cepeda, C.; Gladding, C.M.; Milnerwood, A.J.; Levine, M.S. Pathophysiology of Huntington’s disease: Time-dependent alterations in synaptic and receptor function. *Neuroscience** 2011**, *198*, 252–273. [CrossRef] [PubMed]

62. Ehrlich, M.E. Huntington’s disease and the striatal medium spiny neuron: Cell-autonomous and non-cell-autonomous mechanisms. *Neurotherapeutics* **2012**, *9*, 270–284. [CrossRef]

63. Estrada-Sánchez, A.M.; Rebec, G.V. Corticostriatal dysfunction and glutamate transporter 1 (GLT1) in Huntington’s disease: Interactions between neurons and astrocytes. *Basal. Ganglia* **2012**, *2*, 57–66. [CrossRef] [PubMed]

64. Wood, T.E.; Barry, J.; Yang, Z.; Cepeda, C.; Levine, M.S.; Gray, M. Mutant huntingtin reduction in astrocytes slows disease progression in the BACHD conditional Huntington’s disease mouse model. *Hum. Mol. Genet.* **2019**, *28*, 487–500. [CrossRef]

65. Blumenstock, S.; Dudenova, I. Cortical and striatal circuits in Huntington’s disease. *Front. Neurosci.* **2020**, *14*, 82. [CrossRef]

66. Chan, C.S.; Surmeier, D.J. Astrocytes go awry in Huntington’s disease. *Nat. Neurosci.* **2014**, *17*, 641–642. [CrossRef] [PubMed]

67. Glauser, D.A.; Rossato, J.I.; Bevilaqua, L.R.M.; Cammarota, M. GluN2B and GluN2A-containing NMDAR are differentially involved in extinction memory destabilization and restabilization during reconsolidation. *Sci. Rep.* **2021**, *11*, 186. [CrossRef]

68. Kemper, D.; Costanzo, M.; Jaffe, D.E.; Watanabe, J.I.; Woodard, L.; Levine, M.; Taylor, P.; Elston, R.C.; Miska, E.A.;这款文献与“Page dimensions: 595.3x841.9”无关。
79. Arzberger, T.; Krampfl, K.; Leimgruber, S.; Weindl, A. Changes of NMDA receptor subunit (NR1, NR2B) and glutamate transporter (GLT1) mRNA expression in Huntington’s disease—an in situ hybridization study. J. Neuropathol. Exp. Neurol. 1997, 56, 440–454. [CrossRef]

80. Pietr, G.T.; Schultheiss, L.A.; Hussey, K.C.; Sun, Y.; Dubinsky, J.M.; Aoki, C.; Rosenberg, P.A. Decreased expression of GLT-1 in the R6/2 model of Huntington’s disease does not worsen disease progression. Eur. J. Neurosci. 2013, 38, 2477–2490. [CrossRef]

81. Skotte, N.H.; Andersen, J.V.; Santos, A.; Aldana, B.I.; Willert, C.W.; Norremolle, A.; Waagepetersen, H.S.; Nielsen, M.L. Integrative characterization of the R6/2 mouse model of Huntington’s disease reveals dysfunctional astrocyte metabolism. Cell Rep. 2018, 23, 2211–2224. [CrossRef]

82. Cho, I.K.; Yang, B.; Forest, C.; Qian, L.; Chan, A.W. Amelioration of Huntington’s disease phenotype in astrocytes derived from iPSC-derived neural progenitor cells of Huntington’s disease monkeys. PLoS ONE 2019, 14, e0214156.

83. Dvorzhak, A.; Helassa, N.; Török, K.; Schmitz, D.; Grantyn, R. Single synapse indicators of impaired glutamate clearance derived from fast tGluu imaging of cortical afferents in the striatum of normal and Huntington (Q175) mice. J. Neurosci. 2019, 39, 3970–3982. [CrossRef] [PubMed]

84. Hassel, B.; Tessler, S.; Faull, R.L.; Emson, P.C. Glutamate uptake is reduced in prefrontal cortex in Huntington’s disease. Neurochem. Res. 2008, 33, 232–237. [CrossRef] [PubMed]

85. Garcia, M.; Charvin, D.; Caboche, J. Expanded huntingtin activates the C-Jun N terminal kinase/c-Jun pathway prior to aggregate formation in striatal neurons in culture. Neuroscience 2004, 127, 859–870. [CrossRef] [PubMed]

86. Tong, X.; Ao, Y.; Faas, G.C.; Nwaobi, S.E.; Xu, J.; Haustein, M.D.; Anderson, M.A.; Mody, I.; Olsen, M.L.; Sofroniew, M.V. Astrocyte Kir4.1 channel deficits contribute to neuronal dysfunction in Huntington’s disease model mice. Nat. Neurosci. 2014, 17, 694–703. [CrossRef] [PubMed]

87. Jiang, R.; Diaz-Castro, B.; Looger, L.L.; Khakh, B.S. Dysfunctional calcium and glutamate signaling in striatal astrocytes from Huntington’s disease model mice. J. Neurosci. 2016, 36, 3453–3470. [CrossRef] [PubMed]

88. Bazargani, N.; Attwell, D. Astrocyte calcium signaling: The third wave. Nat. Neurosci. 2016, 19, 182–189. [CrossRef] [PubMed]

89. Garcia, V.J.; Rushton, D.J.; Tom, C.M.; Allen, N.D.; Kemp, P.J.; Svendsen, C.N.; Mattis, V.B. Huntington’s disease patient-derived astrocytes display electrophysiological impairments and reduced neuronal support. Front. Neurosci. 2019, 13, 669. [CrossRef] [PubMed]

90. Shin, J-Y.; Fang, Z.-H.; Yu, Z.-X.; Wang, C.-E.; Li, S.-H.; Li, X.-J. Expression of mutant huntingtin in glial cells contributes to neuronal excitotoxicity. J. Cell Biol. 2005, 171, 1001–1012. [CrossRef] [PubMed]

91. Bankston, A.N.; Mandler, M.D.; Feng, Y. Oligodendroglia and neurotrophic factors in neurodegeneration. Neurosci. Bull. 2013, 29, 216–228. [CrossRef] [PubMed]

92. Myers, R.H.; Vonsattel, J.P.; Paskevich, P.A.; Kiely, D.K.; Stevens, T.J.; Cupples, L.A.; Richardson, E.P., Jr.; Bird, E.D. Decreased neuronal and increased oligodendroglial densities in Huntington’s disease caudate nucleus. J. Neuropathol. Exp. Neurol. 1991, 50, 729–742. [CrossRef] [PubMed]

93. Bartzokis, G.; Lu, P.H.; Tishler, T.A.; Fong, S.M.; Oluwadara, B.; Finn, J.P.; Huang, D.; Bordelon, Y.; Mintz, J.; Perlman, S. Myelin breakdown and iron changes in Huntington’s disease: Pathogenesis and treatment implications. Neurochem. Res. 2007, 32, 1655–1664. [CrossRef] [PubMed]

94. Phillips, O.; Squitieri, F.; Sanchez-Castaneda, C.; Elifani, F.; Caltagirone, C.; Sabatini, U.; Di Paola, M. Deep white matter in Huntington’s disease model mice. PLoS ONE 2014, 9, e109676.

95. Bardile, C.F.; Garcia-Miralles, M.; Caron, N.S.; Rayan, N.A.; Langley, S.R.; Harmston, N.; Rondelli, A.M.; Teo, R.T.Y.; Waltl, S.; Anderson, L.M.; et al. Intrinsically HTT-mediated defects in oligodendroglia cause myelination deficits and behavioral abnormalities in Huntington disease. Proc. Natl. Acad. Sci. USA 2019, 116, 9622–9627. [CrossRef] [PubMed]

96. Huang, B.; Wei, W.; Wang, G.; Gaertig, M.A.; Feng, Y.; Wang, W.; Li, X.J.; Li, S. Mutant huntingtin downregulates myelin regulatory factor-mediated myelin gene expression and affects mature oligodendrocytes. Neuron 2015, 85, 1212–1226. [CrossRef] [PubMed]

97. Wang, N.; Yang, X.W. Huntington disease’s glial progenitor cells hit the pause button in the mouse brain. Cell Stem. Cell 2019, 24, 3–4. [CrossRef] [PubMed]

98. Cui, L.; Jeong, H.; Borovecki, F.; Parkhurst, C.N.; Tanese, N.; Krainc, D. Transcriptional repression of PGC-1alpha by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration. Cell 2006, 127, 59–69. [CrossRef] [PubMed]

99. Johri, A.; Chandra, A.; Beal, M.F. PGC-1α, mitochondrial dysfunction, and Huntington’s disease. Free Radic. Biol. Med. 2013, 62, 37–46. [CrossRef] [PubMed]

100. Xiang, Z.; Valenza, M.; Cui, L.; Leoni, V.; Jeong, H.K.; Brilli, E.; Zhang, J.; Peng, Q.; Duan, W.; Reeves, S.A.; et al. Peroxisome-proliferator-activated receptor gamma coactivator 1α contributes to dysmyelination in experimental models of Huntington’s disease. J. Neurosci. 2011, 31, 9544–9553. [CrossRef] [PubMed]

101. Ryu, H.; Ferrante, R.J. Emerging chemotherapeutic strategies for Huntington’s disease. Expert Opin. Emerg. Drugs 2005, 10, 345–363. [CrossRef] [PubMed]

102. Allis, C.D.; Jenuwein, T. The molecular hallmarks of epigenetic control. Nat. Rev. Genet. 2016, 17, 487–500. [CrossRef] [PubMed]

103. Kuehner, J.N.; Bruggeman, E.C.; Wen, Z.; Yao, B. Epigenetic regulations in neuropsychiatric disorders. Front. Genet. 2019, 10, 268. [CrossRef] [PubMed]

104. Liu, C.; Jiao, C.; Wang, K.; Yuan, N. DNA methylation and psychiatric disorders. Prog Mol. Biol. Transl. Sci. 2018, 157, 175–232. [PubMed]

105. Grayson, D.R.; Guidotti, A. The dynamics of DNA methylation in Schizophrenia and related psychiatric disorders. Neuropsychopharmacology 2013, 38, 138–166. [CrossRef] [PubMed]
106. Suzuki, M.M.; Bird, A. DNA methylation landscapes: Provocative insights from epigenomics. Nat. Rev. Genet. 2008, 9, 465–476. [CrossRef] [PubMed]

107. Ng, C.W.; Yildirim, F.; Yap, Y.S.; Dalin, S.; Matthews, B.J.; Velez, P.J.; Labrador, A.; Housman, D.E.; Fraenkel, E. Extensive changes in DNA methylation are associated with expression of mutant huntingtin. Proc. Natl. Acad. Sci. USA 2013, 110, 2354–2359. [CrossRef]

108. Beal, M.F.; Ferrante, R.J. Experimental therapeutics in transgenic mouse models of Huntington’s disease. Nat. Rev. Neurosci. 2004, 5, 373–384. [CrossRef]

109. Lee, J.; Hwang, Y.J.; Ryu, H.; Kowall, N.W.; Ryu, H. Nucleolar dysfunction in Huntington’s disease. Biochim. Biophys Acta 2014, 1842, 785–790. [CrossRef]

110. Korzus, E.; Rosenfeld, M.G.; Mayford, M. CBP histone acetyltransferase activity is a critical component of memory consolidation. Neuron 2004, 42, 961–972. [CrossRef]

111. Glajch, K.E.; Sadri-Vakili, G. Epigenetic mechanisms involved in Huntington’s disease pathogenesis. J. Huntington. Dis. 2015, 4, 1–15. [CrossRef]

112. Jiang, H.; Potrier, M.A.; Liang, Y.; Pei, Z.; Weiskittel, C.E.; Smith, W.W.; DeFranco, D.B.; Ross, C.A. Depletion of CBP is directly linked with cellular toxicity caused by mutant huntingtin. Neurobiol. Dis. 2006, 23, 543–551. [CrossRef] [PubMed]

113. McFarland, K.N.; Das, S.; Sun, T.T.; Leyer, D.; Xia, E.; Sangrey, G.R.; Kowall, N.W.; Lopes, J.; Luescher, F.; Mau, J.; et al. Genome-wide histone acetylation is altered in a transgenic mouse model of Huntington’s disease. PLoS ONE 2012, 7, e41423. [CrossRef] [PubMed]

114. Sadri-Vakili, G.; Bouzou, B.; Benn, C.L.; Kim, M.O.; Chawla, P.; Overland, R.P.; Glajch, K.E.; Xia, E.; Qiu, Z.; Hersch, S.M.; et al. Histones associated with downregulated genes are hypo-acetylated in Huntington’s disease models. Hum. Mol. Genet. 2007, 16, 1293–1306. [CrossRef]

115. Ryu, H.; Lee, J.; Hargetry, S.W.; Soh, B.Y.; McAlpin, S.E.; Cormier, K.A.; Smith, K.M.; Ferrante, R.J. ESET/SETDB1 gene expression is downregulated in Huntington’s disease models. Proc. Natl. Acad. Sci. USA 2006, 103, 19176–19181. [CrossRef] [PubMed]

116. De Pietri Tonelli, D.; Pulvers, J.N.; Haffner, C.; Murchison, E.P.; Hannon, G.J.; Huttner, W.B. miRNAs are essential for survival and differentiation of newborn neurons but not for expansion of neural progenitors during early neurogenesis in the mouse embryonic neocortex. Development 2008, 135, 3911–3921. [CrossRef] [PubMed]

117. Dong, X.; Cong, S. MicroRNAs in Huntington’s disease: Diagnostic biomarkers or therapeutic agents? Front. Cell. Neurosci. 2021, 15, 313. [CrossRef]

118. Južwik, C.A.; Drake, S.S.; Zhang, Y.; Paradis-Isler, N.; Sylvester, A.; Amar-Zifkin, A.; Douglas, C.; Morquette, B.; Moore, C.S.; Fournier, A.E. microRNA dysregulation in neurodegenerative diseases: A systematic review. Prog. Neurobiol. 2019, 182, 101664. [CrossRef] [PubMed]

119. Sinha, M.; Ghose, J.; Bhattacharyya, N.P. Micro RNA -214,-150,-146a and-125b target Huntingtin gene. RNA Biol. 2011, 8, 1005–1021. [CrossRef]

120. Das, S.; Bhattacharyya, N.P. Heat shock factor 1-regulated miRNAs can target Huntingtin and suppress aggregates of mutant huntingtin. MicroRNA 2015, 4, 185–193. [CrossRef]

121. Kozłowska, E.; Krzyzosiak, W.J.; Koscianska, E. Regulation of huntingtin gene expression by miRNA-137, -214, -148a, and their respective isomiRs. Int. J. Mol. Sci. 2013, 14, 16999–17016. [CrossRef]

122. Bucha, S.; Mukhopadhyay, D.; Bhattacharyya, N.P. Regulation of mitochondrial morphology and cell cycle by microRNA-214 targeting Mitofusin2. Biochem. Biophys Res. Commun. 2015, 465, 795–802. [CrossRef] [PubMed]

123. Ma, B.; Savas, J.N.; Yu, M.-S.; Culver, B.P.; Chao, M.V.; Tanese, N. Huntington mediates dendritic transport of β-actin mRNA in rat neurons. Sci. Rep. 2011, 1, 140. [CrossRef] [PubMed]

124. Caviston, J.P.; Ross, J.L.; Antony, S.M.; Tokito, M.; Holzbaur, E.L. Huntington facilitates dynein/dynactin-mediated vesicle transport. Proc. Natl. Acad. Sci. USA 2007, 104, 10045–10050. [CrossRef] [PubMed]

125. Caviston, J.P.; Holzbaur, E.L. Huntington as an essential integrator of intracellular vesicular trafficking. Trends Cell Biol. 2009, 19, 147–155. [CrossRef] [PubMed]

126. Zala, D.; Hinckelmann, M.-V.; Yu, H.; Da Cunha, M.M.L.; Liot, G.; Cordelierès, F.P.; Marco, S.; Saudou, F. Vesicular glycolysis provides on-board energy for fast axonal transport. Cell 2013, 152, 479–491. [CrossRef] [PubMed]

127. Burke, J.R.; Enghild, J.J.; Martin, M.E.; Jou, Y.-S.; Myers, R.M.; Roses, A.D.; Vance, J.M.; Strittmatter, W.J. Huntingtin and DRPLA proteins selectively interact with the enzyme GAPDH. Nat. Med. 1996, 2, 347–350. [CrossRef]

128. Wu, J.; Lin, F.; Qin, Z. Sequestration of glyceraldehyde-3-phosphate dehydrogenase to aggregates formed by mutant huntingtin. Acta Biochim. Et Biophys. Sin. 2009, 39, 885–890. [CrossRef] [PubMed]

129. Chaudhary, R.K.; Patel, K.A.; Joshi, R.H.; Roy, I. Inhibition of aggregation of mutant huntingtin by nucleic acid aptamers in vitro and in a yeast model of Huntington’s disease. Mol. Ther. 2015, 23, 1912–1926. [CrossRef] [PubMed]

130. Gauthier, L.R.; Charrin, B.C.; Borrell-Pagès, M.; Dompierre, J.P.; Rangone, H.; Cordelierès, F.P.; De Mey, J.; MacDonald, M.E.; Leßmann, V.; Humbert, S. Huntington controls neurotrophic support and survival of neurons by enhancing BDNF vesicular transport along microtubules. Cell 2004, 118, 127–138. [CrossRef] [PubMed]

131. Gauthier, L.; Charpin, B.C.; Borrell-Pagès, M.; Dompierre, J.P.; Rangone, H.; Cordelierès, F.P.; De Mey, J.; MacDonald, M.E.; Leßmann, V.; Humbert, S. Huntington controls neurotrophic support and survival of neurons by enhancing BDNF vesicular transport along microtubules. Cell 2004, 118, 127–138. [CrossRef] [PubMed]

132. Twelvetrees, A.E.; Lesepet, F.; Holzbaur, E.L.; Kittler, J.T. The adaptor proteins HAP1a and GRIP1 collaborate to activate the kinesin-1 isoform KIF5C. J. Cell Sci. 2019, 132, jcs215822. [CrossRef] [PubMed]

133. Collin, E.; Zala, D.; Liot, G.; Rangone, H.; Borrell-Pagès, M.; Li, X.J.; Saudou, F.; Humbert, S. Huntington phosphorylation acts as a molecular switch for anterograde/reterograde transport in neurons. EMBO J. 2008, 27, 2124–2134. [CrossRef] [PubMed]
159. Burtscher, J.; Di Pardo, A.; Maglione, V.; Schwarzer, C.; Squitieri, F. Mitochondrial respiration changes in R6/2 Huntington’s disease model mice during aging in a brain region specific manner. Int. J. Mol. Sci. 2020, 21, 5412. [CrossRef]

160. Cherubini, M.; Lopez-Molina, L.; Gines, S. Mitochondrial fission in Huntington’s disease mouse striatum disrupts ER-mitochondria contacts leading to disturbances in Ca2+ eflux and reactive oxygen species (ROS) homeostasis. Neurobiol. Dis. 2020, 136, 104741. [CrossRef][PubMed]

161. Costa, V.; Giacomello, M.; Hudec, R.; Lopreiato, R.; Ermak, G.; Lim, D.; Malorni, W.; Davies, K.J.; Carafoli, E.; Scorrano, L. Mitochondrial fission and cristae disruption increase the response of cell models of Huntington’s disease to apoptotic stimuli. EMBO Mol. Med. 2010, 2, 490–501. [CrossRef]

162. Damiano, M.; Galvan, L.; Dégol, N.; Brouillet, E. Mitochondria in Huntington’s disease. Biochim. Biophys Acta 2010, 1802, 52–61. [CrossRef][PubMed]

163. Jedrak, P.; Krygier, M.; Tofiska, K.; Drozd, M.; Kaliszewska, M.; Bartnik, E.; Soltan, W.; Sitek, E.J.; Stanislawka-Sachadyn, A.; Limon, J.; et al. Mitochondrial DNA levels in Huntington disease leukocytes and dermal fibroblasts. Metab. Brain Dis. 2017, 32, 1237–1247. [CrossRef]

164. Kim, J.; Moody, J.P.; Edgerly, C.K.; Bordiuk, O.L.; Cormier, K.; Beal, M.F.; Ferrante, R.J. Mitochondrial loss, dysfunction and altered dynamics in Huntington’s disease. Hum. Mol. Genet. 2010, 19, 3919–3935. [CrossRef][PubMed]

165. Song, W.; Chen, J.; Petrilli, A.; Liot, G.; Klinglmayr, E.; Zhou, Y.; Poquiz, P.; Tjong, J.; Pouladi, M.A.; Hayden, M.R.; et al. Mutant huntingtin binds the mitochondrial fission GTPase dynamin-related protein-1 and increases its enzymatic activity. Nat. Med. 2011, 17, 377–382. [CrossRef]

166. Jodeiri Farshbaf, M.; Ghaedi, K. Huntington’s disease and mitochondria. Neurotox. Res. 2017, 32, 518–529. [CrossRef][PubMed]

167. Wang, J.-Q.; Chen, Q.; Wang, X.; Wang, Q.-C.; Wang, Y.; Cheng, H.-P.; Guo, C.; Sun, Q.; Chen, Q.; Tang, T.-S. Dysregulation of mitochondrial calcium signaling and superoxide flashes cause Huntington’s disease through mitochondrial DNA damage. J. Biol. Chem. 2013, 288, 3070–3084. [CrossRef]

168. Elena-Real, C.A.; DiFiglia, M.; Sena-Esteves, M.; Chase, K.; Sapp, E.; Pfister, E.; Sass, M.; Yoder, J.; Reeves, P.; Pandey, R.K.; Rajeev, K.G. Therapeutic silencing of mutant huntingtin with siRNA attenuates striatal and cortical neuropathology and behavioral deficits. Proc. Natl. Acad. Sci. USA 2007, 104, 17204–17209. [CrossRef][PubMed]
184. Yu, D.; Pendergaff, H.; Liu, J.; Kordasiewicz, H.B.; Cleveland, D.W.; Swayne, E.E.; Lima, W.F.; Crooke, S.T.; Prakash, T.P.; Corey, D.R. Single-stranded RNAs use RNAi to potently and allele-selectively inhibit mutant huntingtin expression. *Cell* 2012, 150, 895–908. [CrossRef]

185. McBride, J.L.; Boudreau, R.L.; Harper, S.Q.; Staber, P.D.; Monteys, A.M.; Martins, I.; Gilmore, B.L.; Burstain, H.; Peluso, R.W.; Polisky, B. Artificial miRNAs mitigate shRNA-mediated toxicity in the brain: Implications for the therapeutic development of RNAi. *Proc. Natl. Acad. Sci. USA* 2008, 105, 5868–5873. [CrossRef]

186. Aguiar, S.; van der Gaag, B.; Corsette, F.A.B. RNAi mechanisms in Huntington’s disease therapy: siRNA versus shRNA. *Transl. Neurodegener.* 2017, 6, 30. [CrossRef] [PubMed]

187. Keskin, S.; Brouwers, C.C.; Sogorb-Gonzalez, M.; Martier, R.; Depla, J.A.; Vallés, A.; van Deventer, S.J.; Konstantinova, P.; Evers, M.M. AAV5-miHTT lowers huntingtin mRNA and protein without off-target effects in patient-derived neuronal cultures and astrocytes. *Mol. Ther.-Methods Clin. Dev.* 2019, 15, 275–284. [CrossRef]

188. Mathies, F.; Massari, S.; Bochicchio, A.; Schorpp, K.; Schilling, J.; Weber, S.; Offermann, N.; Desantis, J.; Wanker, E.; Carloni, P.; et al. Reducing mutant huntingtin protein expression in living cells by a newly identified RNA CAG binder. *ACS Chem. Neurosci.* 2018, 9, 1399–1408. [CrossRef]

189. Lopes, C.; Tang, Y.; Anjo, S.I.; Manadas, B.; Onofre, I.; De Almeida, L.P.; Daley, G.Q.; Schlaeger, T.M.; Rego, A.C.C. Mitochondrial and redox modifications in Huntington disease induced pluripotent stem cells rescued by CRISPR/Cas9 CAGs targeting. *Front. Cell Dev. Biol.* 2020, 8, 967. [CrossRef]

190. Dos Santos, N.T.H.; do Bomfim, F.R.C. Gene editing by CRISPR/CAS9 for treatment of Huntington disease. *Int. J. Mol. Sci.* 2020, 21, 38631–38635. [CrossRef] [PubMed]

191. Jamwal, S.; Elsworth, J.D.; Rahi, V.; Kumar, P. Gene therapy and immunotherapy as promising strategies to combat Huntington’s disease-associated neurodegeneration: Emphasis on recent updates and future perspectives. *Expert Rev. Neurother.* 2020, 20, 1123–1141. [CrossRef] [PubMed]

192. Marxreiter, F.; Stemick, J.; Kohl, Z. Huntingtin lowering strategies. *Int. J. Mol. Sci.* 2020, 21, 2146. [CrossRef] [PubMed]

193. Leavitt, B.R.; Kordasiewicz, H.B.; Schobel, S.A. Huntingtonin-lowering therapies for Huntington disease: A review of the evidence of potential benefits and risks. *JAMA Neurol.* 2020, 77, 764–772. [CrossRef]

194. Tabrizi, S.J.; Ghosh, R.; Leavitt, B.R. Huntingtonin lowering strategies for disease modification in Huntington’s disease. *Neuron* 2019, 101, 801–819. [CrossRef] [PubMed]

195. Estevez-Fraga, C.; Flower, M.D.; Tabrizi, S.J. Therapeutic strategies for Huntington’s disease. *Curr. Opin. Neurol.* 2020, 33, 508–518. [CrossRef]

196. Evers, M.M.; Konstantinova, P. AAV5-miHTT gene therapy for Huntington disease: Lowering both huntingtins. *Expert Opin. Biol. Ther.* 2020, 20, 1121–1124. [CrossRef] [PubMed]

197. Barker, R.; Fujimaki, M.; Rogers, P.; Rubinsztein, D. Huntington-in-lowering strategies. *Expert Opin. Investig. Drugs* 2020, 29, 1125–1132. [CrossRef] [PubMed]

198. Smith, A.V.; Tabrizi, S.J. Therapeutic antisense targeting of huntingtin. *DNA Cell Biol.* 2012, 31, 154–158. [CrossRef]

199. Fields, E.; Vaughan, E.; Tripu, D.; Lim, I.; Shrout, K.; Conway, J.; Salib, N.; Lee, Y.; Dhamansia, A.; Jacobsen, M. Gene targeting techniques for Huntington’s disease. *Ageing Res. Rev.* 2021, 70, 101385. [CrossRef]

200. Wild, E.J.; Tabrizi, S.J. Therapeutic DNA targeting in Huntington’s disease. *Lancet Neurol.* 2017, 16, 837–847. [CrossRef]

201. Gardian, G.; Browne, S.E.; Choi, D.-K.; Klibienyi, P.; Gregorio, J.; Kubilus, J.K.; Ryu, H.; Langley, B.; Ratan, R.R.; Ferrante, R.J. Neuroprotective effects of phenylbutyrate in the N171-82Q transgenic mouse model of Huntington’s disease. *J. Biol. Chem.* 2005, 280, 556–563. [CrossRef]

202. Ferrante, R.J.; Kubilus, J.K.; Lee, J.; Ryu, H.; Beesen, A.; Zucker, B.; Smith, K.; Kowall, N.W.; Ratan, R.R.; Luthi-Carter, R. Histone deacetylase inhibition by sodium butyrate chemotherapy ameliorates the neurodegenerative phenotype in Huntington’s disease mice. *J. Neurosci.* 2003, 23, 9418–9427. [CrossRef]

203. Thomas, E.A.; Coppola, G.; Desplats, P.A.; Tang, B.; Soragni, E.; Burnett, R.; Gao, F.; Seeler, J.W.; Furey, K.M.; Borok, J.F.; Herman, D. The HDAC inhibitor 4b ameliorates the disease phenotype and transcriptional abnormalities in Huntington’s disease transgenic mice. *Proc. Natl. Acad. Sci. USA* 2008, 105, 15564–15569. [CrossRef]

204. Jia, H.; Morris, R.M.; Williams, R.M.; Loring, J.F.; Thomas, E.A. HDAC inhibition imparts beneficial transgenerational effects in Huntington disease mice via altered DNA and histone methylation. *Proc. Natl. Acad. Sci. USA* 2015, 112, E56–E64. [CrossRef] [PubMed]

205. Jia, H.; Pallos, J.; Jacques, V.; Lau, A.; Tang, B.; Cooper, A.; Syed, A.; Purcell, J.; Chen, Y.; Sharma, S. Histone deacetylase (HDAC) inhibitors targeting HDAC3 and HDAC1 ameliorate polyglutamine-elicited phenotypes in model systems of Huntington’s disease. *Neurobiol. Dis.* 2012, 46, 351–361. [CrossRef] [PubMed]

206. Siebzehnrubl, F.A.; Raber, K.A.; Urbach, Y.K.; Schulze-Krebs, A.; Canneva, F.; Moceri, S.; Habermeyer, J.; Achoui, D.; Gupta, B.; Steindler, D.A. Early postnatal behavioral, cellular, and molecular changes in models of Huntington disease are reversible by HDAC inhibition. *Proc. Natl. Acad. Sci. USA* 2018, 115, E8765–E8774. [CrossRef]

207. Guedes-Dias, P.; de Proença, J.; Soares, T.R.; Leitão-Rocha, A.; Pinho, B.R.; Duchen, M.R.; Oliveira, J.M. HDAC6 inhibition induces mitochondrial fusion, autophagic flux and reduces diffuse mutant huntingtin in striatal neurons. *Biochim. Et Biophys. Acta (BBA)-Mol. Basis Dis.* 2015, 1852, 2484–2493. [CrossRef] [PubMed]
209. Ferrante, R.J.; Ryu, H.; Kubilus, J.K.; D'Mello, S.; Sugars, K.L.; Lee, J.; Lu, P.; Smith, K.; Browne, S.; Beal, M.F. Chemotherapy for the brain: The antitumor antibiotic mithramycin prolongs survival in a mouse model of Huntington's disease. J. Neurosci. 2004, 24, 10335–10342. [CrossRef] [PubMed]

210. Heiser, V.; Scherzinger, E.; Boeddrich, A.; Nordhoff, E.; Lurz, R.; Lehrach, H.; Wanker, E.E. Inhibition of huntingtin fibrillogenesis by specific antibodies and small molecules: Implications for Huntington's disease therapy. Proc. Natl. Acad. Sci. USA 2000, 97, 6759–6764. [CrossRef] [PubMed]

211. Ferrante, R.J.; Andreassen, O.A.; Jenkins, B.G.; Dedeoglu, A.; Kuemmerle, S.; Kubilus, J.K.; Kaddurah-Daouk, R.; Hersch, S.M.; Beal, M.F. Chemotherapy for Huntington’s disease-related Huntingtin seeding activities in cerebrospinal fluids of Huntington’s disease patients. Sci. Rep. 2020, 10, 20295. [CrossRef] [PubMed]

212. Wei, H.; Qin, Z.-H.; Senatorov, V.; Wei, W.; Wang, Y.; Qian, Y.; Chuang, D.-M. Lithium suppresses excitotoxicity-induced striatal mitochondriaal dystrophy in a transgenic mouse model of Huntington's disease. J. Neurosci. 2016, 20, 4389–4397. [CrossRef] [PubMed]

213. Xu, X.; Ng, B.; Sim, B.; Rudalusec, C.I.; Yusof, N.A.B.M.; Goh, W.L.; Lim, S.; Lim, J.S.Y.; Cha, Y.; Kusko, R.; et al. pS421 huntingtin modulates mitochondrial fission and confers neuroprotection in an HD hPSC model. Cell Death Dis. 2020, 11, 809. [CrossRef] [PubMed]

214. McMeekin, L.J.; Fox, S.N.; Boas, S.M.; Cowell, R.M. Dysregulation of PGC-1α in Huntington’s disease. Cell Chem. Biol. 2019, 26, 5441–5463. [CrossRef] [PubMed]

215. Kratter, I.H.; Zahed, H.; Lau, A.; Tsvetkov, A.S.; Daub, A.C.; Weilert, K.F.; Gu, X.; Saudou, F.; Humbert, S.; Yang, X.W.; et al. Serine 421 regulates mutant huntingtin toxicity and clearance in mice. J. Clin. Investig. 2016, 126, 3585–3597. [CrossRef] [PubMed]

216. Kim, M.; Lee, H.; LaForet, G.; McIntyre, C.; Martin, E.J.; Chang, P.; Kim, T.W.; Williams, M.; Reddy, P.; et al. Disease-related Huntingtin seedling activities in cerebrospinal fluids of Huntington’s disease patients. J. Neurosci. 2019, 19, 964–973. [CrossRef] [PubMed]

217. Xue, X.; Ng, B.; Sim, B.; Rudalusec, C.I.; Yusof, N.A.B.M.; Goh, W.L.; Lim, S.; Lim, J.S.Y.; Cha, Y.; Kusko, R.; et al. pS421 huntingtin modulates mitochondrial fission and confers neuroprotection in an HD hPSC model. Cell Death Dis. 2020, 11, 809. [CrossRef] [PubMed]

218. Kratter, I.H.; Zahed, H.; Lau, A.; Tsvetkov, A.S.; Daub, A.C.; Weilert, K.F.; Gu, X.; Saudou, F.; Humbert, S.; Yang, X.W.; et al. Serine 421 regulates mutant huntingtin toxicity and clearance in mice. J. Clin. Investig. 2016, 126, 3585–3597. [CrossRef] [PubMed]

219. Weber, J.J.; Kloock, S.J.; Nagel, M.; Ortiz-Rios, M.M.; Hofmann, J.; Riess, O.; Nguyen, H.P. Calpastatin ablation aggravates the molecular phenotype in cell and animal models of Huntington disease. Neuropharmacology 2018, 133, 94–106. [CrossRef] [PubMed]

220. Kim, M.; Lee, H.; LaForest, G.; McIntyre, C.; Martin, E.J.; Chang, P.; Kim, T.W.; Williams, M.; Reddy, P.; Tagle, D. Mutant huntingtin expression in clonal striatal cells: Dissociation of inclusion formation and neuronal survival by caspase inhibition. J. Neurosci. 1999, 19, 964–973. [CrossRef] [PubMed]

221. Rieux, M.; Alpaugh, M.; Sciaca, G.; Saint-Pierre, M.; Masnata, M.; Denis, H.L.; Lévesque, S.A.; Herrmann, F.; Bazenet, C.; Garneau, A.P. Shedding a new light on Huntington’s disease: How blood can both propagate and ameliorate disease pathology. Mol. Psychiatry 2020, 25, 739–774. [CrossRef] [PubMed]

222. Ferrante, R.J.; Andreaass, O.A.; Jenkins, B.G.; Dedeoglu, A.; Kueemmerle, S.; Kubilis, J.K.; Kaddurah-Daouk, R.; Hersch, S.M.; Beal, M.F. Neuroprotective effects of creatine in a transgenic mouse model of Huntington’s disease. J. Neurosci. 2000, 20, 4389–4397. [CrossRef] [PubMed]

223. Coroschetz, W.J.; Jenkins, B.G.; Rosen, B.R.; Beal, M.F. Energy metabolism defects in Huntington’s disease and effects of coenzyme Q10. Ann. Neurol. Off. J. Am. Neurol. Assoc. Child. Neurol. 1997, 41, 160–165. [CrossRef] [PubMed]

224. Investigators, H.S.G.P.C. Safety and tolerability of high-dosage coenzyme Q10 in Huntington’s disease and healthy subjects. Mov. Disord. 2010, 25, 1924–1928. [CrossRef] [PubMed]

225. Essa, M.M.; Moghadas, M.; Ba-Omar, T.; Qoronfleh, M.W.; Guillemin, G.J.; Manivasagam, T.; Justin-Thenmozhi, A.; Ray, B.; Bhat, A.; Chidambaram, S.B. Protective effects of antioxidants in Huntington’s disease: An extensive review. Neurotox. Res. 2019, 35, 739–774. [CrossRef] [PubMed]

226. Meekin, L.J.; Fox, S.N.; Boas, S.M.; Cowell, R.M. Dysregulation of PGC-1α-dependent transcriptional programs in neurological and developmental disorders: Therapeutic challenges and opportunities. Cells 2021, 10, 352. [CrossRef] [PubMed]

227. Lopes, C.; Ribeiro, M.; Duarte, A.I.; Humbert, S.; Saudou, F.; De Almeida, L.P.; Hayden, M.; Rege, A.C. IGF-1 intranasal administration rescues Huntington’s disease phenotype in YAC128 mice. Mol. Neurobiol. 2014, 49, 1126–1142. [CrossRef] [PubMed]

228. Martin, D.D.; Ladha, S.; Ehrnhoefer, D.E.; Hayden, M.R. Autophagy in Huntington disease and huntingtin in autophagy. Trends Neurosci. 2015, 38, 26–35. [CrossRef] [PubMed]

229. Lo, C.H.; Pandey, N.K.; Lim, C.K.-W.; Ding, Z.; Tao, M.; Thomas, D.D.; Langen, R.; Sachs, J.N. Discovery of small molecule inhibitors of huntingtin exon 1 aggregation by FRET-Based high-throughput screening in living cells. ACS Chem. Neurosci. 2020, 11, 2286–2295. [CrossRef] [PubMed]

230. Gies, E.; Wilde, I.; Winget, J.M.; Brack, M.; Rotblat, B.; Novoa, C.A.; Balgi, A.D.; Sorensen, P.H.; Roberge, M.; Mayor, T. Niclosamide prevents the formation of large ubiquitin-containing aggregates caused by proteasome inhibition. PLoS ONE 2010, 5, e14410. [CrossRef] [PubMed]

231. Tang, T.S.; Slow, E.; Lupu, V.; Stavrovskaya, I.G.; Sugimori, M.; Llinás, R.; Kristal, B.S.; Hayden, M.R.; Beal, M.F. Beta-propeller protein 3 interacts with Huntingtin and exacerbates Huntington disease-like phenotypes and confers neuroprotection in an HD hiPSC model. Cell Death Dis. 2020, 11, 10262–10274. [CrossRef] [PubMed]

232. Farina, F.; Lambert, E.; Commeau, L.; Lejeune, F.-X.; Roudier, N.; Fonte, C.; Parker, J.A.; Boddart, J.; Verny, M.; Baulieu, E.-E. The stress response factor daf-16/FoxO is required for multiple compound families to prolong the function of neurons with polyglutamine-mediated pathology in a mouse model of Huntington disease. Nat. Med. 1999, 5, 1033–1038. [CrossRef] [PubMed]

233. Zhu, S.; Zhang, Y.; Bai, G.; Li, H. Necrostatin-1 ameliorates symptoms in R6/2 transgenic mouse model of Huntington’s disease. Cell Death Dis. 2011, 2, e115. [CrossRef] [PubMed]
234. Beconi, M.G.; Howland, D.; Park, L.; Lyons, K.; Giuliano, J.; Dominguez, C.; Munoz-Sanjuan, I.; Pacifici, R. Pharmacokinetics of memantine in rats and mice. *PLoS Curr.* 2011, 3, RNN1291. [CrossRef] [PubMed]

235. Reilmann, R.; Ross, C.; Testa, C.; Frank, S.; Evers, M.; de Haan, M.; Valles-Sanchez, A.; Konstantinova, P.; van Deventer, S.; Higgins, J. Translation of AMT-130 preclinical data to inform the design of the first FDA-approved human AAV gene therapy clinical trial in adult with early manifest Huntington’s disease (4531). *Neurology* 2020, 94, 4531.

236. Ehrnhoefer, D.E.; Sutton, L.; Hayden, M.R. Small changes, big impact: Posttranslational modifications and function of huntingtin in Huntington’s disease. *J. Biol. Chem.* 2004, 279, 193–200. [CrossRef] [PubMed]

237. Pandey, M.; Rajamma, U. Huntington’s disease: The coming of age. *J. Genet.* 2004, 73, 419–424. [CrossRef] [PubMed]

238. Tang, B.L. Unconventional secretion and intercellular transfer of mutant huntingtin. *Cells* 2017, 6, 265. [CrossRef] [PubMed]

239. Sanchez, I.; Mahlke, C.; Yuan, J. Pivotal role of oligomerization in expanded polyglutamine neurodegenerative disorders. *Nature* 2003, 427, 373–379. [CrossRef]

240. Rea, S.; Della-Morte, D.; Pacifici, F.; Capuani, B.; Pastore, D.; Coppola, A.; Arriga, R.; Andreadi, A.; Donadel, G.; Di Daniele, N. Pharmacokinetics of Ganglioside GM1 induces phosphorylation of mutant huntingtin and restores normal motor behavior in Huntington disease mice. *Proc. Natl. Acad. Sci. USA* 2012, 109, 3528–3533. [CrossRef] [PubMed]

241. Chen, M.; Ona, V.O.; Li, M.; Ferrante, R.J.; Fink, K.B.; Zhu, S.; Bian, J.; Guo, L.; Farrell, L.A.; Hersch, S.M. Minocycline inhibits caspase-1 and caspase-3 expression and delays mortality in a transgenic mouse model of Huntington disease. *Nat. Med.* 2000, 6, 797–801. [CrossRef]

242. Rea, S.; Della-Morte, D.; Pacifici, F.; Capuani, B.; Pastore, D.; Coppola, A.; Arriga, R.; Andreadi, A.; Donadel, G.; Di Daniele, N. Insulin and exendin-4 reduced mutated Huntingtin accumulation in neuronal cells. *Front. Pharmacol.* 2020, 11, 779. [CrossRef]

243. Di Pardo, A.; Maglione, V.; Alpaugh, M.; Horkey, M.; Atwal, R.S.; Sassone, J.; Ciammola, A.; Steffan, J.S.; Fouad, K.; Truant, R. Ganglioside GM1 induces phosphorylation of mutant huntingtin and restores normal motor behavior in Huntington disease mice. *Proc. Natl. Acad. Sci. USA* 2010, 109, 3528–3533. [CrossRef] [PubMed]

244. Ermak, G.; Hench, K.J.; Chang, K.T.; Sachdev, S.; Davies, K.J. Regulator of calcineurin (RCAN1-11) is deficient in Huntington disease and protective against mutant huntingtin toxicity in vitro. *J. Biol. Chem.* 2009, 284, 11845–11853. [CrossRef]

245. Rangone, H.; Poizat, G.; Troncoso, J.; Ross, C.A.; MacDonald, M.E.; Saudou, F.; Hombert, S. The serum-and glucocorticoid-induced kinase SGK inhibits mutant huntingtin-induced toxicity by phosphorylating serine 421 of huntingtin. *Eur. J. Neurosci.* 2004, 19, 273–279. [CrossRef]

246. Dickey, A.S.; Pineda, V.V.; Tsunemi, T.; Liu, P.P.; Miranda, H.C.; Gilmore-Hall, S.K.; Lomas, N.; Sampat, K.R.; Buttgereit, A.; Torres, M.-J.M. PPAR-δ is repressed in Huntington’s disease, is required for normal neuronal function and can be targeted therapeutically. *Brain Sci.* 2013, 3, 473–479. [CrossRef] [PubMed]

247. Kim, S.J.; Li, J. Caspase blockade induces RIP3-mediated programmed necrosis in Toll-like receptor-activated microglia. *Cell Death Dis.* 2013, 4, e716. [CrossRef] [PubMed]

248. Morikagi, R.; Goto, S. Striatal vulnerability in Huntington’s disease: Neuroprotection versus neurotoxicity. *Brain Sci.* 2017, 7, 63. [CrossRef] [PubMed]

249. Casella, C.; Lipp, I.; Rosser, A.; Jones, D.K.; Metzler-Baddeley, C. A critical review of white matter changes in Huntington’s disease. *Mov. Disord.* 2020, 35, 1302–1311. [CrossRef] [PubMed]

250. Franklin, G.L.; Camargo, C.H.F.; Meira, A.T.; Lima, N.S.; Teive, H.A. The role of the cerebellum in Huntington’s disease: A systematic review. *Cerebellum* 2021, 20, 254–265. [CrossRef]

251. Reiner, A.; Deng, Y.P. Disrupted striatal neuron inputs and outputs in Huntington’s disease. *CNS Neuosci. Ther.* 2018, 24, 250–280. [CrossRef]

252. Wang, H.-M.; Yang, S.; Huang, S.-S.; Tang, B.-S.; Guo, J.-F. Microglial Activation in the Pathogenesis of Huntington’s Disease. *Front. Neurosci.* 2017, 11, 779. [CrossRef]

253. Cepeda, C.; Levine, M.S. Synaptic dysfunction in Huntington’s disease: Lessons from genetic animal models. *Neuroscience* 2020, 1–21. [CrossRef] [PubMed]

254. Tang, B.L. Unconventional secretion and intercellular transfer of mutant huntingtin. *Cells* 2018, 7, 59. [CrossRef]

255. Wanker, E.E.; Ast, A.; Schindler, F.; Trepte, P.; Schnoegel, S. The pathobiology of perturbed mutant huntingtin protein–protein interactions in Huntington’s disease. *J. Neurochem.* 2019, 151, 507–519. [CrossRef]

256. Pandey, M.; Rajamma, U. Huntington’s disease: The coming of age. *J. Genet.* 2018, 97, 649–664. [CrossRef]

257. Tellone, E.; Galtieri, A.; Ficarra, S. Reviewing biochemical implications of normal and mutated Huntingtin in Huntington’s disease. *Curr. Med. Chem.* 2020, 27, 5137–5158. [CrossRef]

258. Ehrnhoefer, D.E.; Sutton, L.; Hayden, M.R. Small changes, big impact: Posttranslational modifications and function of huntingtin in Huntington disease. *Neurosci.* 2011, 17, 475–492. [CrossRef]

259. Soares, T.R.; Reis, S.D.; Pinho, B.R.; Duchen, M.R.; Oliveira, J.M.A. Targeting the proteostasis network in Huntington’s disease. *Ageing Res. Rev.* 2019, 49, 92–103. [CrossRef] [PubMed]

260. Rui, Y.-N.; Xu, Z.; Patel, B.; Cuervo, A.M.; Zhang, S. HTT/Huntingtin in selective autophagy and Huntington disease: A foe or a friend within? *Autophagy* 2015, 11, 858–860. [CrossRef]
292. Rossi, G.; Oh, J.C. Management of agitation in Huntington's disease: A review of the literature. *Curran* 2020, 12, e9748. [CrossRef] [PubMed]

293. Liu, Q.; Cheng, S.; Yang, H.; Zhu, L.; Fan, Y.; Jing, L.; Tang, B.; Li, S.; Li, X.-J. Loss of Hap1 selectively promotes striatal degeneration in Huntington disease mice. *Proc. Natl. Acad. Sci. USA* 2020, 117, 20265–20273. [CrossRef] [PubMed]

294. Yang, H.; Yang, S.; Jing, L.; Huang, L.; Chen, L.; Zhao, X.; Yang, W.; Fan, Y.; Yin, P.; Qin, Z.S.; et al. Truncation of mutant huntingtin in knock-in mice demonstrates exornI huntingtin is a key pathogenic form. *Nat. Commun.* 2020, 11, 2582. [CrossRef]

295. Sharma, M.; Subramaniam, S. Rhes travels from cell to cell and transports Huntington disease protein via TNT-like protrusion. *J. Cell Biol.* 2019, 218, 1972–1993. [CrossRef] [PubMed]

296. Sharma, M.; Rajendrarao, S.; Shahani, N.; Ramirez-Jarquin, U.N.; Subramaniam, S. Cyclic GMP-AMP synthase promotes the inflammatory and autophagy responses in Huntington disease. *Proc. Natl. Acad. Sci. USA* 2020, 117, 15989–15999. [CrossRef] [PubMed]

297. Lee, H.; Noh, J.-Y.; Kim, Y.; Chang, J.-W.; Chung, C.-W.; Lee, S.-T.; Kim, M.; Ryu, H.; Jung, Y.-K. IRE1 plays an essential role in ER stress-mediated aggregation of mutant huntingtin via the inhibition of autophagy flux. *Hum. Mol. Genet.* 2011, 21, 101–114. [CrossRef] [PubMed]

298. Lee, J.; Kosaras, B.; Del Signore, S.J.; Cormier, K.; McKee, A.; Ratan, R.R.; Kowall, N.W.; Ryu, H. Modulation of lipid peroxidation and mitochondrial function improves neuropathology in Huntington's disease mice. *Acta Neuropathol.* 2011, 121, 487–498. [CrossRef] [PubMed]

299. Jeon, G.S.; Kim, K.Y.; Hwang, Y.J.; Jung, M.-K.; An, S.; Ouchi, M.; Ouchi, T.; Kowall, N.; Lee, J.; Ryu, H. Deregulation of BRCA1 leads to impaired spatiotemporal dynamics of γ-H2AX and DNA damage responses in Huntington's disease. *Mol. Neurobiol.* 2012, 45, 550–563. [CrossRef]

300. Hyeon, S.J.; Park, J.; Yoo, J.; Kim, S.-H.; Hwang, Y.J.; Kim, S.-C.; Liu, T.; Shim, H.S.; Kim, Y.; Cho, Y.; et al. Dysfunction of X-linked inhibitor of apoptosis protein (XIAP) triggers neuropathological processes via altered p53 activity in Huntington’s disease. *Prog. Neurobiol.* 2021, 204, 102110. [CrossRef] [PubMed]

301. Mario Isas, J.; Pandey, N.K.; Xu, H.; Teranishi, K.; Okada, A.K.; Fultz, E.K.; Rawat, A.; Applebaum, A.; Meier, F.; Chen, J.; et al. Huntingtonin fibrils with different toxicity, structure, and seeding potential can be interconverted. *Nat. Commun.* 2021, 12, 4272. [CrossRef] [PubMed]

302. Monteiro, O.; Chen, C.; Bingham, R.; Argyrou, A.; Buxton, R.; Jönsson, C.P.; Jones, E.; Bridges, A.; Gattfield, K.; Krauß, S. Pharmacological disruption of the MID1/α4 interaction reduces mutant Huntingtin levels in primary neuronal cultures. *Neurosci. Lett.* 2018, 673, 44–50. [CrossRef]

303. Miyazaki, H.; Yamanaka, T.; Oyama, F.; Kino, Y.; Kurosawa, M.; Yamada-Kurosawa, M.; Yamano, R.; Shimogori, T.; Hattori, N.; Nukina, N. FACS-array-based cell purification yields a specific transcriptome of striatal medium spiny neurons in a murine Huntington disease model. *J. Biol. Chem.* 2020, 295, 9768–9785. [CrossRef]

304. Critchley, B.J.; Isalan, M.; Mielcarek, M. Neuro-cardio mechanisms in Huntington's disease and other neurodegenerative disorders. *Front. Physiol.* 2018, 9, 559. [CrossRef] [PubMed]

305. Hsu, Y.T.; Chang, Y.G.; Chern, Y. Insights into GABA(A)ergic system alteration in Huntington’s disease. *Open Biol.* 2018, 8, 180165. [CrossRef] [PubMed]

306. Burgold, J.; Schulz-Trieglaff, E.K.; Voelkl, K.; Guttiérez-Ángel, S.; Bader, J.M.; Hosp, F.; Mann, M.; Arzberger, T.; Klein, R.; Liebscher, S.; et al. Cortical circuit alterations precede motor impairments in Huntington disease mice. *Sci. Rep.* 2019, 9, 6634. [CrossRef] [PubMed]

307. Raj, A.; Powell, F. Network model of pathology spread recapitulates neurodegeneration and selective vulnerability in Huntington’s Disease. *NeuroImage* 2021, 235, 118008. [CrossRef] [PubMed]

308. Lebouc, M.; Richard, Q.; Garret, M.; Baufreton, J. Striatal circuit development and its alterations in Huntington’s disease. *Neurobiol. Dis.* 2020, 145, 105076. [CrossRef] [PubMed]

309. Federspiel, J.D.; Greco, T.M.; Lum, K.K.; Cristea, I.M. Hdac4 interactions in Huntington’s disease viewed through the prism of multimics. *Mol. Cell Proteom.* 2019, 18, S92–S113. [CrossRef] [PubMed]

310. Cheng, J.; Liu, H.P.; Lin, W.Y.; Tsai, F.J. Identification of contributing genes of Huntington’s disease by machine learning. *BMC Med. Genom.* 2020, 13, 176. [CrossRef]

311. Seefelder, M.; Kochanek, S. A meta-analysis of transcriptomic profiles of Huntington's disease patients. *PLoS ONE* 2021, 16, e0253037. [CrossRef]

312. Imamura, T.; Fujita, K.; Tagawa, K.; Ikura, T.; Chen, X.; Homma, H.; Tamura, T.; Mao, Y.; Taniguchi, J.B.; Motoki, K.; et al. Identification of hepta-histidine as a candidate drug for Huntington's disease by in silico-in vitro-in vivo-integrated screens of chemical libraries. *Sci. Rep.* 2016, 6, 33861. [CrossRef] [PubMed]

313. Kumar, S.; Panwar, S.; Sharma, M.K.; Sharma, M.K. Genes to drug: An in-silico approach to design a drug for Huntington disease (HD) in Homo sapiens. *Int. J. Comput. Biol. Drug Des.* 2021, 14, 190–201. [CrossRef]

314. Kohli, H.; Kumar, P.; Ambasta, R.K. In silico designing of putative peptides for targeting pathological protein Htt in Huntington’s disease. *Heliyon* 2021, 7, e06088. [CrossRef] [PubMed]

315. Sundaram, J.R.; Wu, Y.; Lee, I.C.; George, S.E.; Hota, M.; Ghosh, S.; Kesavapany, S.; Ahmed, M.; Tan, E.K.; Shenalikut, S. PromISR-6, a guanabenz analogue, improves cellular survival in an experimental model of Huntington's disease. *ACS Chem. Neurosci.* 2019, 10, 3575–3589. [CrossRef] [PubMed]

316. Deepa, S.; Rymbai, E.; Praveen, T.; Saravanan, J. Neuroprotective effects of farnesol on motor and cognitive impairment against 3-nitropropionic acid-induced Huntington’s disease. *Thai J. Pharm. Sci.* 2021, 45, 16–23.