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Targeting Glial Cells to Elucidate the Pathogenesis of Huntington's Disease

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Abstract Huntington's disease (HD) is a hereditary neurodegenerative disorder caused by expended CAG repeats in the Huntingtin (Htt) gene. The resultant mutant Htt (mHtt) forms aggregates in neurons and causes neuronal dysfunctions. The major characteristic of HD is the selective loss of neurons in the striatum and cortex, which leads to movement disorders, dementia, and eventual death. Expression of mHtt was also found in non-neuronal cells in the brain, suggesting non-cell-autonomous neurotoxicity in HD. As was documented in many different neurodegenerative disorders, elevated inflammatory responses are also reported in HD. To date, effective treatments for this devastating disease remain to be developed. This review focuses on the importance of glial cells and inflammation in HD pathogenesis. Potential anti-inflammatory interventions for HD are also discussed.

Keyword Huntington's disease · Astrocytes · Glia · Inflammation · Neurodegenerative disorder

Abbreviations

Aβ	Amyloid β peptide
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
BDNF	Brain-derived neurotrophic factor
CNS	Central nervous system
GLT1	Astroglial glutamate transporter
Htt	Huntingtin
HD	Huntington's disease
mHtt	Mutant Htt
iNOS	Inducible nitric oxide synthase
NO	Nitric oxide
polyQ	Polyglutamine
ROS	Reactive oxygen species
WT	Wildtype

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Huntington's Disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease initially described by George Huntington in 1872 [1]. The major characteristic of HD is the selective loss of neurons in the striatum and cortex, which leads to movement disorders, dementia, and eventual death. The causative mutation is a CAG trinucleotide expansion in exon 1 of the Huntingtin (Htt) gene, which is translated into a polyglutamine (polyQ) tract. When the number of CAG repeats exceeds 36, Htt forms aggregates in the nuclei and cytoplasm of neurons, glia, and several other types of peripheral cells (e.g., liver, muscle, and adipocytes), hijacks a wide variety of proteins, and eventually causes neuronal degeneration and metabolic dysfunctions [2–10]. The expanded CAG repeats of Htt may also acquire toxic functions and evoke cell loss in HD. Normal Htt exists ubiquitously in the body with the highest level in the brain [11], and plays central roles in intracellular vesicle transport and transcription [12, 13]. Accumulating evidence demonstrates that the polyQ-expanded mutant (m)Htt disrupts the functions of normal Htt. For example, mHtt suppresses vesicle transport and thus disturbs the secretion of an essential neurotrophic

factor (brain-derived neurotrophic factor, BDNF) [14]. In spite of extensive research efforts in the past, an effective treatment against this dreadful disease is still not available at present. Of 22 clinical trials (1,254 HD patients), only one drug (tetrabenazine) recently approved by the Food and Drug Administration of USA showed a clear positive effect of controlling the chorea symptoms of HD [15]. Much to the dismay of HD patients and their families, no pharmacological intervention from eight trials (1,366 HD patients) was proven to be effective in delaying the progression of HD [16].

Aggregates of mHtt can be found in the nuclei, cytoplasm, and axonal terminals of affected neurons as a result of insufficient protein degradation [6, 17–19]. Increased clearance of mHtt therefore might ameliorate cellular dysfunctions and neurodegeneration in HD. Jeong et al. recently demonstrated that enhanced acetylation of mHtt at K444 facilitated the trafficking of mHtt into autophagosomes, improved clearance of mHtt by macroautophagy, and eventually reversed the toxic effects in primary striatal neurons and in a transgenic *Caenorhabditis elegans* model of HD. [20]. Moreover, elevated oxidative stress is believed to play a critical role in HD pathogenesis [21]. Interestingly, many signal transduction pathways are altered in HD. For example, signals of several G protein-coupled receptors in the brains of HD mice were amplified when compared to wildtype (WT) mice [22–24]. The ability of HD neurons to regulate post-endocytic recycling of plasma membranes is also impaired [25]. Most importantly, profound changes in the electrophysiological properties of neurotransmitter receptors in HD mice were noted [26, 27]. The sensitivity of NMDA receptors in the corticostriatal pathway is markedly increased before significant neuronal cell loss occurs during HD progression [28]. HD neurons also respond to glutamate with higher Ca^{2+} signaling and apoptosis [29]. The above finding is very similar to that found in neurons expressing polyQ-expanded spinocerebellar atrophy type 2 (SCA2) [30], suggesting that the existence of aggregates and/or misfolded proteins weakens the calcium homeostasis of neurons and reduces their ability to survive. Since the surroundings of neurons play a critical role in regulating neuronal activities, the interplay between neurons and other brain cells in HD has begun to attract attention. Although mHtt is known to induce neuronal atrophy, most studies emphasized the effects of mHtt on neurons with little attention being paid to glial cells. Herein, we review the importance of glial Htt in HD pathogenesis (Fig. 1).

Astrocytes in HD and Neurodegenerative Disorders

Besides neurons, mHtt was also found in other brain cells including glial cells [31–33]. Although marked astrogliosis and microgliosis were reported in brains of HD patients and HD mice [34–38], the functions and regulations of glial cells in HD progression were never extensively characterized until very recently [31, 32]. In the brain, astrocytes are the largest cell population and play multiple roles. The functions of astrocytes include promoting neuronal survival and plasticity, removing toxic materials (e.g., glutamate and free radicals), providing gliotransmitters to neurons through neuronal–glial interactions, and regulating the blood-brain barrier and immune defense in the central nervous system (CNS) [39, 40]. Dysfunction of astrocytes was shown to induce neurotoxic effects in several neurodegenerative diseases [39, 41–43]. Upon stimulation with proinflammatory mediators, astrocytes become reactivated (i.e., astrogliosis) with increases in proliferation, cell hypertrophy, and astroglial markers (e.g., GFAP, vimentin, S-100, and glutamine synthetase) [40, 42]. Impairment of glutamate transporters in damaged astrocytes usually causes elevations in the levels of synaptic glutamate and excitotoxicity [44]. As documented in many neurodegenerative diseases, neurons inevitably become more vulnerable to toxic insults [31, 45, 46] in the presence of mutant astrocytes. For example, reduction of an astrocytic glutamate transporter (EAAT2) is a common feature in both familial and sporadic amyotrophic lateral sclerosis (ALS) [47, 48]. In HD, Lievenet al. reported that expression of astroglial glutamate transporter (GLT)-1 was lower in brains of a transgenic mouse model of HD (R6/2 mice). Glutamate uptake was thus proposed to be defective in HD mice compared to WT mice [49]. Indeed, it was later found that mHtt suppresses glutamate uptake in primary astrocytes which reduces their ability to protect neurons from excitotoxicity [31]. Most importantly, transgenic mice expressing mutant Htt in astrocytes exhibit multiple symptoms of HD (viz., body weight loss, motor function deficits, and shorter lifespans), demonstrating that expression of mutant Htt in astrocytes is sufficient to cause neurological symptoms [50]. Fowler et al. recently showed that striatal release of ascorbate, which is highly dependent on glutamate uptake, in R6/2 mice was markedly lower than that of WT mice. This finding further supports the existence of a glutamate uptake defect in the striatum of HD mice [51]. The resultant overactive glutamate system is believed to greatly worsen neuronal degeneration in HD, especially when HD neurons are much more vulnerable to glutamate-induced apoptosis [29]. Since medium spiny neurons in the striatum are innervated by glutamatergic neurons from the cortex, they are particularly vulnerable to glutamate-induced excitotoxicity. Downregulation of GLT-1 in astrocytes may provide a possible pathogenic mechanism for the selective degeneration of MSNs in the striatum of mice and patients with HD.

In addition to the clearance of damaging materials, astrocytes also have important roles in neuronal protection. For instance, astrocytes release glutathione which makes neurons less susceptible to reactive oxygen species (ROS)

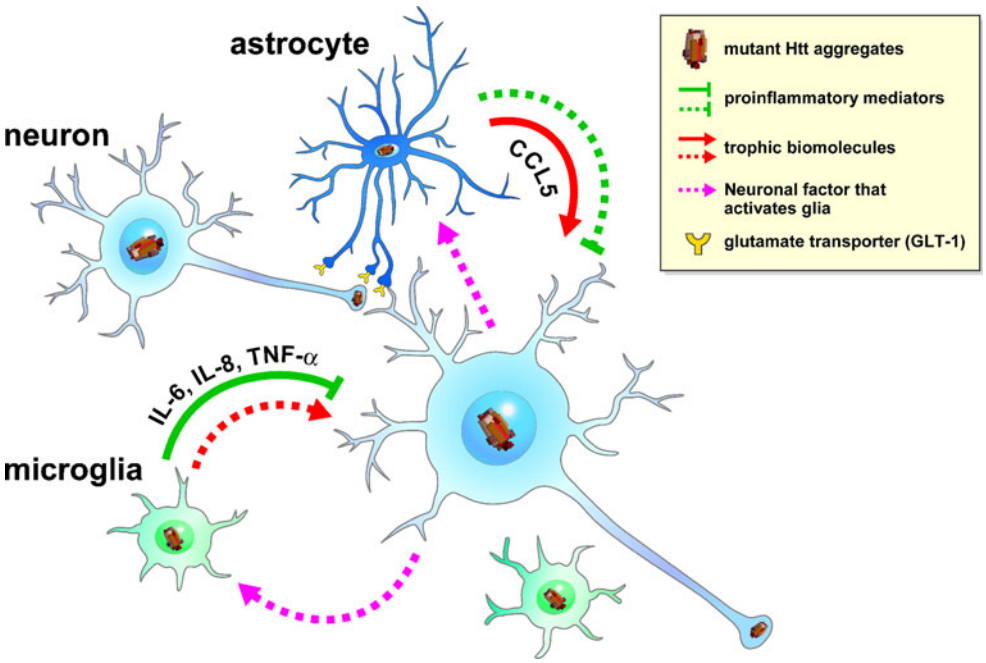

Fig. 1 Altered neuronal–glial interactions in Huntington's disease. Aggregates of mutant Huntingtin (*mHtt*) exist in neurons, astrocytes, and microglia. Astrocytes that express mHtt contain fewer glutamate transporters, and are less capable of protecting neurons from glutamate excitotoxicity [31]. On top of this astrocytic defect, neurons expressing mHtt are more sensitive to glutamate-induced apoptosis [29]. Furthermore, expression of mHtt in astrocytes also weakens their ability to produce CCL5/RANTES for neurons, thus causing neuronal degeneration [32]. mHtt enhances the ability of microglia to produce proinflammatory mediators (including IL-6, IL-8, and TNF-α) and might contribute to neurodegeneration in HD [33]. *Dotted lines* indicate additional potential neuronal–glial interactions that might also be altered in HD

and thus protects them from ROS-induced death [52]. Moreover, astrocytes are able to secrete a number of neurotrophic factors (including glial cell-line-derived neurotrophic factor and BDNF) to support the functions and survival of neurons. Drugs that increase the release of neurotrophic factors in astrocytes were shown to protect dopaminergic neurons against lipopolysaccharide- or MPTP-induced neurotoxicity [53–55]. One major class of mediators for astrocytes comprises the chemokine family. We recently reported that mHtt was expressed in astrocytes and suppressed the availability of astrocytic CCL5/RANTES to neurons through at least two different mechanisms: reduced transcription and defective release [32]. CCL5/RANTES is an important chemokine and is known to exhibit diverse functions including modulation of neuronal migration, regulation of proliferation and/or differentiation of astrocytes, and mediation of inflammation in neuronal diseases [56–58]. We demonstrated that mHtt reduced the NF-κB-mediated expression of CCL5/RANTES at the transcriptional level in astrocytes, as well as retained the residual CCL5/RANTES inside astrocytes. Defects in releasing sufficient amounts of CCL5/RANTES by astrocytes in HD might cause degeneration of neuronal processes (e.g., shorter neurites and a fewer number of spines), altered neuronal properties, and degenerated motor coordination as reported elsewhere [59, 60]. The observed defect in releasing CCL5/RANTES in the primary astrocyte culture of HD suggests a dysregulation of calcium-dependent neuronal–glial interactions in HD [32].

Microgliosis in HD and Neurodegenerative Disorders

Marked astrogliosis and microgliosis are detected in the caudate and internal capsule of HD patients [34] but not in the normal brain. Microglia are resident macrophages in the brain and are implicated in several neurodegenerative diseases [61–63]. In the brain, microglia mainly exist in a resting state. Upon stress, microglia sense the signal and migrate to damaged sites [64]. During neuronal injury, the role of microglia is controversial because they can provide trophic molecules (e.g., neurotrophins) to support neuronal survival as well as release neurotoxic molecules (e.g., nitric oxide (NO), and proinflammatory cytokines) [65]. In Alzheimer's disease (AD), amyloid β peptide (Aβ) accumulation stimulates microglia to release inflammatory mediators (e.g., NO, TNFα, IL-1β, and ROS) [66–71] which are likely to produce detrimental effects. In addition to inflammatory mediators, complement activation is another pathogenic process implicated in AD progression

[72]. Activated microglia are associated with the products of complement activation and the membrane attack complex (MAC) on amyloid plaques and degenerating neurons [70, 71]. Complement activation promotes phagocytosis and facilitates cell lysis by the MAC [73]. Another important damaging insult from activated microglia comes from ROS [74]. In particular, the function of NADPH in activated microglia was vigorously investigated. NADPH oxidase is known to form a complex at plasma membranes by assembling gp91phox and p22phox with phosphorylated p47phox, and then converting oxygen to superoxide radicals ($O2^-$) upon microglial activation [75]. Increased ROS production during inflammation by NADPH oxidase may evoke mitochondrial dysfunction and neuronal death [76, 77]. Drugs aimed at modulating microglial activation have been actively evaluated for several degenerative disorders.

In the brains of HD mice and patients, aggregates of mHtt are found in dysregulated microglial cells which exhibit thick and distorted processes [36]. Expression of inducible nitric oxide synthase (iNOS, a key player in inflammation) is also observed in microglia at the symptomatic stage of HD mice [78]. Most importantly, activation of microglia can be observed at the presymptomatic stage [36, 37], suggesting that microglial activation is an early incident in the progression of HD. Moreover, microglial activation appears to be correlated with the severity of the disease in both HD patients and mice [36, 79]. Activation of microglia therefore might play a critical role in the pathogenesis of HD.

Consistent with the importance of microglia, altered immune profiles in plasma and striatal tissue were recently documented in HD [33]. Levels of proinflammatory cytokines (IL-6, IL-8, and TNF-α) in the plasma and cerebrospinal fluid of HD patients were higher than those of non-HD controls. Importantly, levels of proinflammatory cytokines of HD patients correlate with HD progression [33]. In addition, increased complement biosynthesis (e.g., of C3 and C9) by microglia was observed in brains of HD patients. It was proposed that complements produced locally by microglia are activated on the membranes of neurons to induce cytotoxicity of neurons, and may contribute to neuronal death [34].

Inflammation and Neurodegenerative Diseases

Inflammation in the brain is a common feature of various neurodegenerative diseases including AD, Parkinson's disease (PD), ALS, and HD [80–87]. The neuroinflammatory machinery therefore is an important drug target for many degenerative diseases [48, 85, 88–93]. For instance, minocycline was shown to produce beneficial effects in animal models of AD and ALS through, at least partly, an anti-inflammatory mechanism [94]. In the brain, the major cell types responsible for inflammatory responses are astrocytes and microglia which release inflammatory mediators (e.g. cytokines, chemokines, and reactive free radicals) upon stimulation [95]. In AD, accumulation of Aβ is associated with neuroinflammation in the brain, and therefore is considered a proinflammatory event. Deposition of Aβ induces microglial activation followed by the recruitment of astrocytes, and this eventually leads to the production and release of proinflammatory cytokines and neurotoxic materials. Similarly, a marked increase in the number of reactive microglia was found in the brains of PD patients and MPTP-treated animals [96, 97]. In PD, many noxious factors (e.g., cytokines, reactive oxygen intermediates, and NO) are released by microglia and cause damage to dopaminergic neurons. Together, microglia and astrocytes are believed to significantly contribute to the neurotoxicity of various brain diseases. It should also be noted that neuroinflammation is a double-edged sword [98]. Many studies suggested that neuroinflammation plays a detrimental role in neurodegenerative diseases [99, 100], while other studies indicated that inflammation is neuroprotective under certain circumstances [101, 102]. For example, although inflammation was shown to produce detrimental consequences in AD, studies using animal models of AD suggest that certain inflammatory responses are beneficial in stimulating Aβ clearance [98]. When glial activation fails to clear the toxic forms of Aβ, the innate immune response becomes chronic and neurotoxic [103]. Although the importance of inflammation in HD has been postulated for many years, it was not actively investigated until recently as detailed above. Treatments aimed at inflammation remain to be developed and validated. Several laboratories have evaluated the beneficial effects of minocycline (a well-established anti-inflammatory reagent) in different genetic mouse models of HD, but found controversial results [104–106]. The disease stage, the drug administration protocol, and the animal models might play critical roles in evaluating the therapeutic potential of anti-inflammatory drugs.

Concluding Remarks

HD is a devastating genetic disease with no effective cure at present [16]. After the first genetic mouse model of HD was created [107], tremendous amounts of information regarding HD pathogenesis accumulated. Besides the well-established degenerative mechanisms found in neurons of HD, the most exciting findings in non-neuronal cells of HD to date include the astrocytic deficiency of glutamate uptake [31] and inferior neurotrophic support of neurons by astrocytes [32]. Overactivation of microglia in HD also attracted much attention which led to the possibility of developing treat-

ments to prevent microglial activation in HD [108]. Given the importance of inflammation in most neurodegenerative disorders, the inflammatory responses in the CNS and immune system of HD are of great interest. To obtain mechanistic insights into neuronal inflammation, it is critical to observe interactions between neurons and glial cells in both in vivo and in vitro settings. Notably, studies from several laboratories recommended NF-κB as an attractive drug target for HD because it is involved in neuroinflammation by glial cells as well as in the production and release of the neurotrophic CCL5/RANTES by astrocytes [32, 33]. Characterization of the roles of NF-κB in different populations of brain cells in HD is obviously a timely task, and will pave the way for developing anti-inflammatory interventions for HD and bringing novel insights into understanding the disease progression of HD.

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