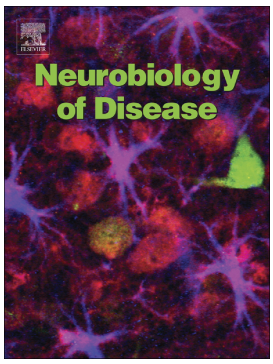

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The contribution of glial cells to Huntington's disease pathogenesis

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Abstract

Glial cells play critical roles in the normal development and function of neural circuits, but in many neurodegenerative diseases, they become dysregulated and may contribute to the development of brain pathology. In Huntington's disease (HD), glial cells both lose normal functions and gain neuropathic phenotypes. In addition, cell-autonomous dysfunction elicited by mutant huntingtin (mHTT) expression in specific glial cell types is sufficient to induce both pathology and Huntington's disease–related impairments in motor and cognitive performance, suggesting that these cells may drive the development of certain aspects of Huntington's disease pathogenesis. In support of this, imaging studies in pre-symptomatic HD patients and work on mouse models have suggested that glial cell dysfunction occurs at a very early stage of the disease, prior to the onset of motor and cognitive deficits. Furthermore, selectively ablating mHTT from specific glial cells or correcting for HD-induced changes in their transcriptional profile rescues some HD-related phenotypes, demonstrating the potential of targeting these cells for therapeutic intervention. Here we review emerging research focused on understanding the involvement of different glial cell types in specific aspects of HD pathogenesis. This work is providing new insight into how HD impacts biological functions of glial cells in the healthy brain as well as how HD induced dysfunction in these cells might change the way they integrate into biological circuits.

Keywords

Huntington's disease, mutant huntingtin, glia, astrocytes, microglia, oligodendrocytes, pericytes, cell-autonomous, pathogenesis, physiology, myelin

Introduction

Huntington's disease is a devasting monogenetic neurodegenerative condition characterized by movement disorders, cognitive deficits, and psychiatric symptoms. Affected individuals normally become symptomatic in the 3rd or 4th decade of life, with relentless progression thereafter. There

are currently around 30,000 symptomatic individuals in the United States alone, with a further 200,000 individuals at risk (Huntington's disease Society of America. Overview of HD).

Pioneering studies in the 1980's and early 1990's showed that HD is caused by a single dominant allele of the huntingtin gene containing an expanded number of CAG repeats (Gusella et al., 1983). Since then, there have been extensive efforts to understand the molecular, cellular, and system-level changes that occur during the disease and how these contribute to the development of motor, cognitive, and behavioral deficits. These include but are not limited to the generation of a wide range of animal and cellular models, strategies to restrict expression of the mutant protein to different cell types, unbiased transcriptomic and proteomic approaches to identify molecular changes, and strategies to identify differences in the way brain regions are connected as the disease progresses (Bradford et al., 2009; Cepeda et al., 2010; Chan et al., 2015; Chang et al., 2015b; Consortium, 2017; Crotti et al., 2014; Espinoza et al., 2018; Gu et al., 2005; Huang et al., 2015; Lahr et al., 2018; Langfelder et al., 2016; McColgan et al., 2017; Rosas-Arellano et al., 2018; Wang et al., 2014a; Yan et al., 2018). While these efforts have greatly enhanced our understanding of the molecular mechanisms underlying different pathological processes, they have not yet led to the development of an effective therapy.

One important unanswered question is how the ubiquitous expression of the mutant huntingtin gene leads to selective degeneration of specific brain regions, cell types, and synaptic connections. Brain imaging and molecular studies in both mice and humans have shown that the basal ganglion suffers the most significant volume changes, transcriptional alterations, and cellular loss (Aylward et al., 1994; Aylward et al., 1996; Aylward et al., 1997; Langfelder et al., 2016; Myers et al., 1991; Vonsattel et al., 1985). Indeed, even within this structure, specific neuronal subtypes and synaptic connections seem to be selectively vulnerable, especially at the early stages of disease (Hong et al., 2012; McColgan et al., 2017; Milnerwood and Raymond, 2007; Poudel et al., 2015; Zheng and Kozloski, 2017). At least one factor that may be limiting our understanding of how selective pathology develops is the fact that glial cell populations in these brain regions have not been extensively studied. Changes in neuronal biology including altered morphologies, transcriptional profiles, electrical properties, and network functions have been well documented in multiple HD models (Cowan and Raymond, 2006; Espinoza et al., 2019; Gu et al., 2005; Han et al., 2010; Mehta et al., 2018; Merienne et al., 2019; Milnerwood and Raymond, 2010; Raymond et al., 2011; Trushina et al., 2004; Wang et al., 2014a; Zheng and Kozloski, 2017). In contrast, the abnormalities that occur in different glial cell populations, including loss of normal function and gain of neuropathic

phenotypes and how these might impact the observed neuronal changes, are only now beginning to be understood.

In this review, we highlight our current understanding of glial cell dysfunctions in HD that have been gained from studies using model organisms as well as interrogations of human disease. We also discuss the cell-autonomous pathologies elicited by mHTT expression in specific glial cell types as well as the HD phenotypes that are resolved through the removal of mHTT from these cells (Table 1). Finally, we outline some of the questions that remain and suggest some approaches to address these.

Astrocytes

Astrocytes play a number of important roles in the development and functioning of the nervous system including maintaining extracellular ion balance, supporting synaptogenesis, carrying out necessary developmental synaptic elimination, clearing neurotransmitters, supplying nutrients to neurons, stabilizing the blood brain barrier, and regulating behaviors such as sleep and grooming (Abbott et al., 2006; Allen, 2014; Allen and Eroglu, 2017; Chung et al., 2013; Haydon, 2016; Haydon, 2017; Plog and Nedergaard, 2018; Stogsdill and Eroglu, 2017; Yu et al., 2018). Their activities are critical to maintaining the electrical properties of neuronal membranes and enabling synaptic signaling. As such, disrupting their functions not only affects neuronal circuits but also leads to the development of abnormal behaviors (Lee et al., 2014; Nagai et al., 2019; Yu et al., 2018).

<u>Huntington's disease changes astrocyte size and function as well as their interactions with neuronal circuits</u>

Striatal astrocytes show a marked change in morphology in HD mouse models (Table 2) prior to the onset of motor and cognitive deficits. Both dye-filling and viral-labelling approaches in the R6/2 HD model (in which a mutated form of the N-terminal fragment of human huntingtin is expressed) have found a substantial reduction in astrocyte surface area (Octeau et al., 2018). A phenotype that has also been displayed by human astrocytes expressing mHTT following transplantation of their progenitor cells into the corpus callosum of the mouse brain (Osipovitch et al., 2019). In addition, a recent study using a novel fluorescence resonance energy transfer (FRET)–based proximity reporter assay termed NAPA (neuron astrocyte proximity assay), in which relevant fluorophores are genetically targeted to different neuronal and astrocyte populations, found that the relative proximity of astrocyte processes to striatal inputs coming from different brain regions also changes in R6/2 HD mice (Octeau et al., 2018). Striatal astrocyte processes have reduced association with cortico-striatal inputs, a selectively vulnerable population of synaptic connections that, in HD mouse models and human disease,

show dysfunction prior to symptom onset. In contrast, their association to thalamo-striatal connections, the other major source of excitatory input into the striatum, is increased (Octeau et al., 2018). The functional significance of these altered structural associations is not yet clear, but one possibility is that diminished astrocyte support of cortico-striatal inputs leads to their dysfunction and eventual loss from the striatum. This theory is supported by studies showing that activity at the neuronal synapse can regulate the structure of perisynaptic astrocyte processes, leading to changes in their degree of synaptic coverage, which then ultimately feeds back onto mechanisms that control the stability of dendritic spines (Bernardinelli et al., 2014; Perez-Alvarez et al., 2014).

Along with changes in cell structure, striatal astrocytes in HD mice adopt an altered transcriptional profile. Using a viral-mediated approach to isolate RNA from astrocytes with RiboTag technology (in which ribosomes are tagged with a hemagglutinin epitope to enable their isolation), Diaz-Castro et al. found significant changes in astrocyte expression profiles in mouse HD models that increased in magnitude with disease progression (Diaz-Castro et al., 2019) (Table 2). Transcripts for K+ channels, the components of calcium signaling mechanisms, and neurotransmitter transporters are downregulated, whereas transcripts associated with deoxyribonucleic acid (DNA) packaging, metabolism, and cell signaling are increased. Some of these transcriptional changes are also observed in post-mortem tissue from HD patients, although their attribution to astrocytes remains to be confirmed (Diaz-Castro et al., 2019). One study has partially addressed this by interrogating the transcriptional profile of cultured human astrocytes derived from glial progenitor cell lines expressing mHTT. They also found elements of calcium signaling pathways to be disrupted as well as genes associated with synaptic function, endosomal transcripts, cell-cell junctions and extracellular matrix components (Osipovitch et al., 2019). However, it remains to be determined whether these changes also occur in HD patients and how they are impacted by clinical progression of the disease and the development of other aspects of pathology.

Astrocytes in HD mice also display a number of abnormalities in their electrical properties. These likely affect their ability to maintain ion homeostasis and have been shown to affect the release of glutamate and adenosine triphosphate (ATP), which impacts neuronal signaling (Xiong et al., 2018; Yang et al., 2019) (Table 2). Using patch clamp recordings, Tong et al. found that, in the R6/2 mouse model, striatal astrocytes are significantly more depolarized and have a higher membrane resistance, a measure that relates to changes in cell size as well as the number of open ion channels (Tong et al., 2014). Interestingly, these changes appear to be region specific, with no abnormalities observed in hippocampal astrocytes (Tong et al.,

2014). Using the calcium indicator GCaMP3 to monitor spontaneous activity in striatal astrocytes from R6/2 mice, others have shown that, despite these cells displaying the normal forms of spontaneous calcium signaling seen in wild-type (WT) mice, these events are significantly reduced in amplitude, duration, and frequency (Jiang et al., 2016). In contrast, the calcium signaling responses induced by stimulating cortico-striatal signaling in brain slices are greater, suggesting that astrocytes are becoming more responsive to neuronal signaling (Jiang et al., 2016). The consequences of these changes to spontaneous and evoked calcium signaling in astrocytes and how they might impact Huntington's disease pathogenesis are still unclear. However, a recent study highlighted the important role $Ca2^+$ signaling in astrocytes plays in communication between neuronal populations. Yu and colleagues demonstrated that specifically altering $Ca2^+$ signaling in striatal astrocytes is sufficient to not only affect signaling between striatal and cortical neuronal populations but also self-grooming behavior in WT mice (Yu et al., 2018). Interestingly, this self-grooming behavior is also observed in HD mice at a very early stage of the disease, before the onset of motor deficits, and can be reversed by a blocker of Solute Carrier Family 6 Member 11 (GAT-3), a gamma aminobutyric acid (GABA) transporter that shows enriched expression in astrocytes. Other aspects of motor dysfunction, such as limb clasping, forelimb grip strength, and walking stride, are however not rescued by this intervention (Yu et al., 2018).

Importantly, not only have the temporal and dynamic aspects of changes to the electrical properties of astrocytes been demonstrated in HD mouse models, but progress has been made in identifying some of the molecular events underlying them. Using pharmacological strategies to isolate specific potassium channels in astrocytes, Tong and colleagues found that currents of inward rectifying ATP-sensitive inward Rectifier Potassium Channel 10 (Kir4.1) channels, which are key regulators of the resting membrane potential of astrocytes and important players in regulating extracellular levels of K^+, are reduced in two different HD mouse models (Tong et al., 2014) (Table 2). This reduction is matched by a fall in striatal protein levels of this channel and driven by a specific depression of Kir4.1 levels in those astrocytes containing mutant huntingtin aggregates. Importantly, viral-based strategies to restore Kir4.1 levels in astrocytes normalize the resting membrane potentials of these cells and restore the magnitude of some spontaneous Ca2+ currents, demonstrating that changes in the levels of this protein are sufficient to drive at least some of the electrophysical deficits observed (Tong et al., 2014).

Excitingly, restoring Kir4.1 levels in astrocytes not only improves astrocyte-specific deficits but also rescues some of the electrophysiological abnormalities observed in the medium spiny neuron (MSN) population in the striatum (Tong et al., 2014). In many different HD model

mice, MSNs have increased membrane potential, reduced rheobase (the minimum current amplitude applied over 300 milliseconds that is sufficient to depolarize a cell), and increased input resistance, which together indicate a more excitable state (Cepeda et al., 2010). Strikingly, these parameters were at least partially returned to normal WT levels following astrocyte-specific elevation of Kir4.1. This may be, in part, due to a normalization of elevated extracellular K^+ levels, as increasing K^+ levels in WT brain slices reproduces some of the MSN excitability features seen in R6/2 mice (Tong et al., 2014). While this intervention only elicits moderate rescue of motor deficits, mice do have an increased lifespan (Tong et al., 2014). A recent study using an AAV9 construct to enable the virus to be delivered systemically replicated some of these findings, with a reduction in the excitability of MSNs and an improvement in excessive circling behavior (Vagner et al., 2016). While the importance of Kir4.1 to the development of HD pathology has been clearly demonstrated in mouse models other members of the inwardly rectifying KCNJ family as well as KCNQ leak channels show dysregulated expression in human astrocytes expressing mHTT (Osipovitch et al., 2019). As such their potential contribution to HD pathology should also be investigated in appropriate model systems.

In addition to Kir 4.1, changes in the level of glutamate uptake receptor 1 (GLT-1) in astrocytes have also been implicated in the development of electrophysiological abnormalities in HD mouse models (Jiang et al., 2016). In both mouse models and human postmortem HD tissue, the levels of GLT-1 are significantly reduced, and it is thought this may underlie the increase in evoked calcium signaling in astrocytes (Arzberger et al., 1997; Bradford et al., 2009; Jiang et al., 2016; Lievens et al., 2001) (Table 2). In support of this theory WT mice treated with a specific pharmacological inhibitor of GLT-1 display a similar change in the magnitude of their evoked $Ca2^+$ signaling. These results also implicate glutamate uptake as a key regulator of astrocyte engagement in the cortico-striatal circuit (Jiang et al., 2016). Interestingly, restoring Kir4.1 levels using a viral-mediated approach also rescues GLT-1 expression in astrocytes, perhaps explaining why Kir4.1-treated R6/2 mice also have partial recovery of their response to evoked cortico-striatal signaling (Jiang et al., 2016). There is also evidence that, like Kir4.1, restoring GLT-1 levels can have beneficial effects on some of the behavioral phenotypes observed in HD mice. Treating R6/2 mice with ceftriaxone, a β lactam antibiotic that elevates GLT-1 expression, is sufficient to reduce the elevated level of extracellular glutamate and suppress HD-related behaviors including paw clasping while also improving motor performance in plus maze and open-field climbing paradigms (Miller et al., 2008). However, it is important to point out that others have found that genetic ablation of one copy of GLT-1 in the R6/2 model does not exacerbate motor deficits or impact the weight loss normally seen in this model (Petr et

al., 2013). This suggests that the either the effect of GLT-1 on these phenotypes is non-linear and thus a small reduction contributes to reduced performance but further incremental reductions do not or that ceftriaxone could be exerting it's beneficial effects through other mechanisms.

While changes in Kir4.1 and GLT-1 levels in HD astrocytes clearly play a part in the development of electrical abnormalities in these cells, spontaneous calcium signals are only partially rescued through Kir4.1 and GLT-1 elevation, suggesting that there are likely other molecular changes that contribute to these deficits (Jiang et al., 2016). Given the exciting finding that restoring some of the homeostatic electrical properties of astrocytes can not only rescue electrical deficits in neurons but also abrogate HD-related behaviors, this will be an important area for future study.

Dysfunctional astrocyte metabolism

There is a growing body of evidence that the metabolic function of astrocytes and their production of key neuronal metabolites are also perturbed in Huntington's disease. A recent study employing ^{13}C-labelled energy substrates and gas chromatography mass spectroscopy to quantify their incorporation into cellular metabolites found that the tricarboxylic acid cycle is likely impaired in the striatal astrocytes of R6/2 mice (Skotte et al., 2018) (Table 2). Using brain slices and [1,2-^{13}C] acetate, which is metabolized preferentially in astrocytes, Skotte and colleagues showed that incorporation of ^{13}C into ketoglutarate, aspartate, and glutamate, which are key components of the tricarboxylic acid cycle, is significantly reduced. ^{13}C labelling of glutamine, a precursor of neuronal GABA that is exclusively synthesized by astrocytes and then transported to neurons, is also reduced (Skotte et al., 2018).

In addition to glutamine, the secretion of cholesterol by astrocytes is also impaired in HD (Valenza et al., 2015). Cholesterol is required for neuronal function, and its depletion leads to dendritic spine degeneration, failed neurotransmission, and decreased synaptic plasticity (Zhang and Liu, 2015). Cultured astrocytes overexpressing full-length human mHTT and primary astrocytes from R6/2 mice both have reduced levels of cholesterol biosynthetic gene transcripts as well as impaired cellular production and secretion of cholesterol and apolipoprotein E (APOE) (Valenza et al., 2015). Intriguingly, strategies to enhance cholesterol biosynthesis in HD astrocytes by overexpressing sterol regulatory element binding transcription factor 2 (SREBP2), a master regulator of cholesterol biosynthesis, are sufficient to overcome a neurite outgrowth deficit seen in HD neurons. In addition, application of exogenous cholesterol restored some of the perturbed electrical properties of these cells (Valenza et al., 2015). While

the significance of these findings has yet to be tested *in vivo*, it is likely that altered astrocyte metabolism is another factor that contributes to pathology in HD mouse models.

Mutant huntingtin expression in astrocytes is sufficient to drive HD pathology

While many features of astrocyte biology are disrupted in Huntington's disease, work is still ongoing to determine which of these are due to the pathological effects of mHTT expression in this cell type. A study by Bradford and colleagues found that expressing full-length human mHTT with 160 CAG repeats under the control of the glial fibrillary acidic protein (GFAP) promoter (which drives expression in some astrocyte populations) induces at least some HD behavioral phenotypes including increased hind paw clasping and impaired motor performance on the rotarod (Bradford et al., 2009). It also causes a significant reduction in body weight and life expectancy. In addition, as observed in the other HD models, expression of the glutamate transporter GLT-1 is reduced (Bradford et al., 2009). A separate study using a lentiviral vector to induce mHTT expression specifically in striatal astrocytes also found reduced GLT-1 levels as well as reduced levels of dopamine- and cyclic-AMP-regulated phosphoprotein of molecular weight 32,0000 (DARPP-32) and N-methyl D-aspartate receptor subtype 2B (NR2B), two neuronal proteins that are expressed at a lower level in multiple HD mouse models (Faideau et al., 2010).

Not only is mHTT expression in astrocytes sufficient to induce neuropathology and behavioral deficits, its specific genetic ablation from this cell type partially slows or prevents aspects of the disease in HD mice. Wood and colleagues used a tamoxifen Cre–mediated system to specifically remove the mutant huntingtin gene from GFAP-expressing astrocytes in the BACHD mouse model of HD, reducing overall mHTT levels in the striatum by 40% (Wood et al., 2019). This reduction was paralleled by a slower decline in motor performance in the rotarod paradigm and a partial abrogation of a depressive behavioral phenotype. Interestingly, anxiety phenotypes were not resolved, suggesting that these may involve neuronal circuits that are not directly influenced by the pathological effects of mHTT expression in astrocytes (Wood et al., 2019). Alongside improvements in behavior, there was a significant increase in striatal volume as well as levels of the post-synaptic marker postsynaptic density protein 95 (PSD-95). Strikingly, patch clamp recordings of MSNs showed that the magnitude of evoked N-methyl-D-aspartate receptor (NMDAR) currents were also normalized following genetic ablation of astrocyte mutant huntingtin (Wood et al., 2019).

While these results are intriguing, it is important to note that many aspects of HD neuropathology have not yet been assessed in these mice. In addition, the temporal precision offered by the tamoxifen Cre means that future studies could assess whether genetically

removing mHTT in astrocytes at different stages of disease progression elicit the same level of behavioral and neuropathological rescue. To this end, a recent study showed that zinc finger protein transcriptional repressors designed to reduce *mHTT* expression could be targeted to astrocytes in the adult mouse using a viral-mediated approach. The authors found this suppresses the appearance of mHTT aggregates in these cells as well as rescues HD-associated astrocyte transcriptional changes (Diaz-Castro et al., 2019). This demonstrates another way in which the cell-autonomous functions of mHTT expression in astrocytes could be further explored in a tightly regulated temporal manner.

Cell-autonomous effects of mHTT expression are also observed in human astrocytes. Human HD glial chimeras, generated by neonatally engrafting immunodeficient mice with human glial progenitor cells (hGPCs) expressing mHTT, develop aspects of HD neuropathology including abnormal neuronal physiology and impaired motor performance (Benraiss et al., 2016). In the reverse experiment, in which hGPCs expressing WT huntingtin are grafted into the striatum of the R6/2 HD mouse model, several aspects of pathology are reduced. The hyper-excitable neuronal phenotype resolves, and the loss of functional inputs normally observed in this model is prevented. In addition, transplanted mice have an almost complete rescue of striatal volume and improvements in motor and cognitive performance in the rotarod and water T maze, respectively. Perhaps most strikingly, transplanted mice have a significant increase in life expectancy (Benraiss et al., 2016). It still remains to be determined whether donor glia are eliciting their beneficial effects by restoring normal cell function, as observed in mouse astrocytes following strategies to restore Kir4.1 and GLT-1 levels, or whether the presence of persistent glial progenitor cells has a gain of function effect through undetermined mechanisms. Regardless, future studies like this will help deepen our understanding of human glial dysfunction.

Human disease

The ways in which astrocytes are impacted by and contribute to pathology in human disease remain relatively underexplored due to the limited availability of post-mortem tissue at different disease stages as well as the lack of imaging agents that can interrogate molecular changes in HD patients. Despite this, there have been important observations made that correlate with some of the key findings described in model organisms. First, there is a neuropathological grade–dependent reduction in GLT1 protein levels, which has important roles in determining the astrocytic response to cortico-striatal signaling in mouse models of HD (Arzberger et al., 1997; Faideau et al., 2010). Second, transcriptomic studies have shown that levels of Kir4.1 mRNA,

another driver of some of the electrophysiological abnormalities seen in HD astrocytes, are lower in post-mortem tissue from HD patients (Hodges et al., 2006).

In addition to these shared molecular changes, astrogliosis, the name given to a complex and poorly understood process in which astrocytes adopt a reactive state at both later stages of disease progression in HD mouse models and following conditional deletion of the WT huntingtin protein, is also seen in post-mortem tissue from HD patients (Faideau et al., 2010; Gu et al., 2015; McKinstry et al., 2014; Sofroniew, 2014; Tong et al., 2014). Faideau and colleagues found that the density of GFAP staining, a marker of astrogliosis, increases with neuropathological grade (a measure that is based on striatal atrophy and neuron loss) in human post-mortem tissue (Faideau et al., 2010). While the impact of this on the neuropathological changes observed in Huntington's disease is currently unknown, there is a particular type of neurotoxic reactive astrocyte state, termed A1, whose transcriptional signature is enriched in HD brains with high neuropathological grades (Diaz-Castro et al., 2019; Liddelow et al., 2017). Culture experiments and acute injury paradigms have shown that adoption of this reactive state has a detrimental effect on a number of normal astrocyte functions including their role in the formation of neuronal synaptic structures. Its enrichment in HD tissue could therefore indicate a role for A1 astrocytes in the development of some aspects of pathology (Liddelow et al., 2017). However, further experiments will be required to determine whether and how the A1 astrocyte transcriptional signature (or other astrocyte states) identified in post-mortem HD tissue contributes to specific aspects of HD pathogenesis or circuit dysfunction. It should also be noted that there is a significant enrichment of markers of another less well understood but putatively neuroprotective reactive astrocyte state termed A2 in HD tissue of the same neuropathological grade (Diaz-Castro et al., 2019). Untangling the relative contributions of different reactive astrocyte states (there are likely to be many more that remain unidentified) and their distributions will therefore be important in understanding the role astrocytes play in the progression of neuropathology at later stages of the disease.

Microglia

Microglia are the resident macrophages of the CNS and play important and diverse roles in brain development and function including regulating aspects of neurogenesis, promoting oligodendrocyte maturation and myelination, and sculpting and refining neuronal circuits during development (Cunningham et al., 2013; Hagemeyer et al., 2017; Hammond et al., 2018; Pang et al., 2013; Ribeiro Xavier et al., 2015; Squarzoni et al., 2014; Wlodarczyk et al., 2017). These cells have highly motile processes that contact neurons and synaptic elements in a dynamic

manner that is regulated by neuronal activity (Akiyoshi et al., 2018; Bernier et al., 2019; Davalos et al., 2005; Liu et al., 2019; Nimmerjahn et al., 2005; Stowell et al., 2019). Microglia also promote the function and development of neuronal connections through the release of neuroactive signals and the removal of excess synapses (Akiyoshi et al., 2018; Filipello et al., 2018; Lehrman et al., 2018; Paolicelli et al., 2011; Schafer et al., 2012; Weinhard et al., 2018). Importantly, genetic or pharmacological disruption or elimination of microglia is sufficient to alter the number of synapses in the adult and induce changes in both neural circuitry and behavior (Filipello et al., 2018; Ji et al., 2013; Nelson and Lenz, 2017; Paolicelli et al., 2011; Parkhurst et al., 2013; Schafer et al., 2012; Torres et al., 2016; Zhan et al., 2014).

Huntington's disease changes microglial morphology and motility

In both mouse models of HD and human disease, microglia adopt a more ameboid morphology, with increased soma size and fewer primary processes (Franciosi et al., 2012; Sapp et al., 2001; Savage et al., 2020; Simmons et al., 2007) (Table 2). These changes occur very early in the development of brain pathology and are observed in mouse models that specifically recapitulate aspects of the early stages of human disease as well as low neuropathological grade human HD tissue (as defined by neuronal loss and tissue atrophy). They also occur in the absence of significant changes in microglial cell number (Diaz-Castro et al., 2019; Franciosi et al., 2012). While the functional significance of morphology changes has never been fully explored in any biological context, this data implies that microglia enter a different state early in the disease process.

Positron emission tomography (PET) studies using radiolabeled ligands to the peripheral benzodiazepine receptor (PBR) also known as the 18 kDa translocator protein (TSPO), have also found early changes in microglial biology in Huntington's disease patients. PBR is a five-transmembrane mitochondrial protein that plays a role in a variety of key cellular processes including neurosteroid synthesis, maintenance of the mitochondrial membrane potential, $Ca2^{+}$ homeostasis, and energy metabolism (Bader et al., 2019; Bonsack and Sukumari-Ramesh, 2018). In Huntington's disease, increased PBR-dependent PET signals have been observed in disease-affected brain regions, such as the striatum, amygdala, and frontal cortex, prior to the onset of motor and cognitive symptoms and correlate with clinical metrics of disease progression (Pavese et al., 2006; Politis et al., 2015; Politis et al., 2011; Tai et al., 2007). However, care should be taken in attributing these signals exclusively to microglia, because while these cells do increase their expression of PBR following exposure to signals, such as lipopolysaccharides (LPS), PBR PET tracers can bind to astrocytes and PBR is expressed by some populations of neurons and endothelial cells (Beckers et al., 2018; Betlazar et al., 2018;

Rashid et al., 2018). Thus, highlighting the need for the development of new imaging markers that are specific for both glial cell types and their functional states.

In addition to structural changes, microglial cells isolated from HD mice have reduced baseline process motility and slower responses to chemo-attractant cues (Table 2). Using a Boyden chamber paradigm, Kwan et al. isolated primary microglia from the brains of HD mice and monocytes from the blood of HD patients and found that their migration in response to the chemoattractant cues adenosine triphosphate (ATP), complement component 5a (C5a), and monocyte chemoattractant protein-1 (MCP-1) was reduced despite the expression of their respective receptors being unchanged (Kwan et al., 2012b). Furthermore, in vivo live-cell imaging using fractalkine receptor (Cx3CR1) green fluorescent protein (GFP) reporter mice showed that the baseline extension and retraction of microglial processes in the cortex, which are normally highly dynamic, are significantly reduced in HD mice. In addition, their process migration in response to focal laser ablation injury is significantly slower. This may, in part, be due to lower levels of microglial cofilin, a mediator of actin cytoskeleton dynamics, although this remains to be tested experimentally with pharmacological or genetic rescue strategies (Kwan et al., 2012b). Interestingly, there is a relationship between neuronal activity and microglial dynamics, which operates through noradrenergic signaling. It may be therefore that the aberrant neuronal activity reported in the striatum of HD mice also plays a role in microglial motility deficits (Liu et al., 2019; Stowell et al., 2019). While the functional significance of microglial process motility and microglia migration in response to cues are still being explored, recent studies have suggested that microglial contact with neuronal elements influences neurite outgrowth, enhances the probability of spine elimination at specific developmental stages, and promotes dendritic calcium activity (Akiyoshi et al., 2018; Wake et al., 2009). It will be interesting to see whether any or all of these phenotypes are disrupted in HD.

Elevated expression of inflammatory cytokines in Huntington's disease

Together with changes in morphology and motility, microglia in HD mice also upregulate their expression of pro-inflammatory cytokines, though the specific cytokines and time points at which they are observed vary between studies (likely due to the differences in the transgenic model being examined or the method of analysis). Tumour necrosis factor alpha (Tnfα), interleukin 6 (IL-6), interleukin 10 (IL-10), interleukin 1 beta (IL-1β), and interleukin 12 (IL-12) are all elevated in the striatum of either the R6/2, YAC128, or zQ175 HD mouse models at the end stage of the disease (Kwan et al., 2012a; Pido-Lopez et al., 2018). In addition, while it still remains to be determined whether microglia are the sole source of these elevated cytokine levels, Crotti et al. found that transcripts for IL-6 are elevated in primary microglia isolated from the brains of zQ175

mice (Crotti et al., 2014) (Table 2). Separately, Pido-Lopez and colleagues using clodronate to deplete immune cell populations demonstrated that myeloid cells (of which microglia are the brain-resident population) and dendritic cells drive the elevated plasma concentrations of cytokines IL1β, interleukin 2 (IL2), IL6, and Tnfα (Pido-Lopez et al., 2018).

While the molecular mechanisms underlying upregulated cytokine expression have not been fully explored, a recent study suggested that microglial expression of galectin-3 (LGALS3), a member of the lectin family that interacts with glycoproteins on cell surfaces, plays an important role in driving the elevation of cytokine levels in the R6/2 mouse model of HD. Siew et al. found that transcript and protein levels of LGALS3 were elevated in the striatum of R6/2 mice, and a combination of IHC, FACS, and RTPCR on isolated primary cells suggested that this increase was primarily a result of enhanced microglial expression (Siew et al., 2019). Strategies to lower LGALS3 expression in primary microglia derived from HD mice or *in vivo* using short hairpin ribonucleic acid (shRNA)-mediated or pharmacological approaches are sufficient to lower the levels of a number of inflammatory cytokines, including IL-6, TNFα, and NO, and boost the levels of the anti-inflammatory IL-10 (Siew et al., 2019). This is very much in line with other studies demonstrating that LGALS3 regulates cytokine release in response to a variety of inflammatory cues and pathological contexts (Chen et al., 2015; Jeon et al., 2010). Intriguingly, intra-striatal delivery of shLgals3, which reduces the levels of *LGALS3* transcripts, before the onset of behavioral deficits is sufficient to completely prevent deterioration of motor performance in the rotarod paradigm and significantly extend lifespan. However, the gradual loss of body weight normally observed in this HD model is not rescued. Treatment also normalized levels of the striatal marker DARPP32 as well as other microglial lysosomal proteins (Siew et al., 2019). While these interesting findings suggest that LGALS3 could be an attractive microglial molecule to target for therapeutic intervention, care should be taken in concluding that all of the reported beneficial effects are due to a reduction in cytokine levels. Given the diverse functions of microglia in health and disease, a more careful exploration of the molecular mechanisms underlying these effects is warranted.

Levels of inflammatory cytokines are also increased in post-mortem tissue from HD patients. Silvestroni and colleagues found that interleukin 10 (IL10), chemokine (C-C Motif) ligand 2 (CCL2), IL-6, interleukin 8 (IL-8), and matrix metalloproteinase 9 (MMP9) are all increased in the striatum, cortex, and cerebellum (Silvestroni et al., 2009). In addition, there is some evidence that inflammatory cytokines and immune cell chemokines are elevated much earlier in the progression of the disease, as higher levels have been observed in both the blood and cerebrospinal fluid (CSF) of HD patients prior to the onset of clinical symptoms (Bjorkqvist

et al., 2008; Chang et al., 2015a; Rodrigues et al., 2016). However, as in the mouse, it has yet to be established that microglia are the cellular source of these cytokines. More importantly, while some studies have demonstrated that elevated cytokine levels can be neurotoxic under certain circumstances, others have found that cytokines can play a beneficial role in the promotion of nerve repair (Chien et al., 2016; Leibinger et al., 2016; Yang et al., 2012; Zigmond, 2011; Zigmond, 2012). It thus remains to be determined how cytokines are acting in HD and the impact they might have on the development of HD-related neuropathology and behavioral deficits.

Cell-autonomous actions of mHTT in microglia

It is clear that microglia do not simply respond to mHTT induced pathology in other cell types however the impact of mHTT expression on their biology and the ways in which this might contribute to the development of different aspects of Huntington's disease pathology are still being uncovered. Using a microglial cell line, Crotti et al. found that mHTT expression increases the levels of the pro-inflammatory cytokines IL6 and TNFα and that this is driven through the actions of the PU.1 and C/EPB transcription factors (Crotti et al., 2014). Similar changes are observed in the transcriptional profile of microglia isolated from HD mice. However, further investigation will be required to ascertain whether these are due to the cell-autonomous actions of mHTT expression or a response of microglia to the development of brain pathology (Crotti et al., 2014). In addition to the enhanced expression of cytokines, transfection of myeloid cell lines with mHTT impairs their migration response to chemoattractant cues. Both of these phenotypes can be rescued in HD mice using genetic strategies to specifically ablate *mHTT* in myeloid cells (Kwan et al., 2012b; Petkau et al., 2019).

In terms of the broader impact of microglial mHTT on the development of brain pathology Crotti et al. demonstrated that the expression of mHTT specifically in myeloid cells, including microglia, causes neuronal damage when a mouse is exposed to an inflammatory stimulus. Using a *Cx3cr1 Cre*–mediated approach to 'knock in' exon 1 of mutant huntingtin, they found that, following a stereotactic injection of LPS, microglia induced a greater amount of Fluorojade B staining, a marker of neuronal damage (Crotti et al., 2014). In contrast, a more recent study by Petkau and colleagues, in which a genetic approach was used to lower but not eliminate mHTT in myeloid cells using *Lys2 Cre*, found that, while the enhanced secretion of inflammatory cytokines by microglia in response to a stimulus was ablated, aspects of motor performance were not rescued. Using both the rotarod and open-field paradigms, they found that partially reducing mHTT expression in myeloid cells did not improve latency to fall from the rod or the total distance travelled. It also did not rescue reductions in total brain and forebrain

weight observed in this HD model or reductions in striatal and cortical volume (Petkau et al., 2019).

Unfortunately, the limitations of both these studies, including the fact that mHTT expression was only partially reduced in Petkau, the fact that both genetic strategies targeted all myeloid cells, and that only a limited number of HD-related phenotypes were investigated, make it impossible to come to any definitive conclusion as to whether microglial mHTT expression plays a role in HD-related pathologies. It seems very likely given the human imaging and cytokine profiling studies in pre-symptomatic HD patients that microglia are at the very least associated with and responding to some of the earliest pathological events in HD (Bjorkqvist et al., 2008; Chang et al., 2015a; Pavese et al., 2006; Politis et al., 2015; Politis et al., 2011; Rodrigues et al., 2016; Tai et al., 2007).

Given the important role microglia play in refining and sculpting neuronal connections as well as their involvement in pathological synapse elimination, future studies investigating the impact of HD-related microglial dysfunction on neuronal physiology, circuits and behavior will be crucial in gaining greater insight into the role of microglia in HD (Filipello et al., 2018; Hong et al., 2016; Lehrman et al., 2018; Lui et al., 2016; Norris et al., 2018; Paolicelli et al., 2011; Salter and Stevens, 2017; Schafer et al., 2016; Schafer et al., 2012; Vasek et al., 2016; Weinhard et al., 2018). Indeed, there is increasing evidence from a number of mouse models of neurodegenerative disease that complement proteins, components of the innate immune system, and microglia co-ordinate to mediate synaptic elimination in a variety of pathological contexts (Dejanovic et al., 2018; Hong et al., 2016; Norris et al., 2018; Vasek et al., 2016; Wu et al., 2019). As the expression of complement proteins has also been shown to be increased in post-mortem tissue from HD patients this could be a relevant area to study in the context of HD pathogenesis (Agus et al., 2019; Hodges et al., 2006; Labadorf et al., 2015).

Finally, recent studies demonstrating that signaling between microglia and astrocytes can alter molecular and functional states suggests that further exploration of the involvement of both cell types in HD-related pathologies should address whether this crosstalk is important to the pathological mechanisms being described (Liddelow et al., 2017; Shinosaki et al., 2017).

Oligodendrocytes

Oligodendrocytes are the myelinating glia of the CNS. They wrap around axons and form the myelin sheaths necessary for rapid transmission of electrical signals between neurons. This process can be highly dynamic and contribute to circuit plasticity, with visual stimuli and enrichment leading to changes in oligodendrocyte proliferation and differentiation as well as subtly changing myelin properties in specific synaptic pathways (Almeida and Lyons, 2017;

Chorghay et al., 2018; de Hoz and Simons, 2015; Etxeberria et al., 2016). In addition to their critical role in providing myelin sheaths, oligodendrocytes in combination with astrocytes provide trophic support for neurons through the delivery of metabolites, such as pyruvate and lactate, and promote neurite outgrowth in specific contexts (Meyer et al., 2018; Philips and Rothstein, 2017; Saab et al., 2016; Simons and Nave, 2015).

Mouse models of HD reveal deficits in oligodendrocyte biology and myelination

In mouse models of HD, morphological and molecular assessments have found that structural impairments in myelin are present early in the disease, before the onset of motor and cognitive deficits (Garcia-Miralles et al., 2019; Jin et al., 2015; Teo et al., 2016). Electron microscopy studies have found that myelin sheaths in the corpus callosum are significantly thinner and have reduced compaction even at 1 month of age (Teo et al., 2016) (Table 2). The early time point at which these myelination deficits appear could indicate an impairment in oligodendrocyte differentiation or a failure of oligodendrocytes to wrap axons and initiate myelination. However, studies have found no difference in the number of myelinated axons in the corpus callosum of HD mice and no decrease in the total number of oligodendroglial cells or proliferating oligodendrocyte precursor cells in the corpus callosum or white matter tracts of the striatum, even at 12 months of age (Ferrari Bardile et al., 2019; Garcia-Miralles et al., 2019; Jin et al., 2015). Instead, the expression of myelin-related genes is significantly reduced in both striatal and cortical tissues. This correlates with comparable reductions in the expression of these genes by oligodendrocytes isolated from HD mice, suggesting that this deficit is at least in part due to mHTT expression in this cell type (Ferrari Bardile et al., 2019; Garcia-Miralles et al., 2019; Jin et al., 2015; Teo et al., 2016). While these myelination deficits do not impact the conduction velocity of axons in the corpus callosum, it is highly likely that they do impair transmission of information across neuronal circuits, as evidenced by the impairments in motor performance when mHTT is expressed specifically in oligodendroglial cells and the rescue of several HD-related pathologies when it is genetically excised from this population in HD mice (see below) (Ferrari Bardile et al., 2019; Huang et al., 2015). Future studies to investigate this further and to look at the impact of potential impairments in olidodendroglial metabolic support of neurons are warranted given the early dysfunction of this cell type in HD mice.

In addition to underlying impairments in both myelin ultrastructure and gene expression, oligodendrocytes in HD mice are less able to respond to a demyelinating injury. Teo and colleagues found that, six weeks after treatment with the demyelinating agent cuprizone, mature oligodendrocytes in the corpus callosum of HD mice have significantly less recovery in numbers compared to their WT littermates, despite the fact that populations in both mice decline to

similar levels immediately following cuprizone treatment. Both ultra-structure measures of the percentage of myelinated axons and FlouroMyelin intensity measurements of myelin levels also show that remyelination is impaired in HD mice (Teo et al., 2019).

Cell-autonomous actions of mHTT in oligodendrocytes

In line with the cell-autonomous actions of mHTT in astrocytes and microglia, expression of the mutant gene in oligodendroglial lineage cells alters oligodendrocyte biology and induces neuropathological and behavioral deficits. Huang and colleagues expressed an N-terminal fragment of mHTT under the control of the myelin proteolipid protein (*PLP)* promotor to restrict expression to cells in the oligodendroglial lineage (Huang et al., 2015). While this had no effect on the number of oligodendrocytes present in the cortex of these mice, the myelin sheaths of axons in the striatum were significantly thinner at 5 months of age. This was accompanied by a dysregulated expression of genes involved with lipid metabolism and a reduction in the levels of myelin proteins, including cyclic nucleotide 3' phosphodiesterase (CNP), myelin basic protein (MBP), myelin associated oligodendrocytic basic protein (MOBP), and myelin oligodendrocyte glycoprotein (MAG), in the striatum and brain stem at 1 month of age. The authors suggest this may, in part, be due to a preferential binding of mHTT to the transcription factor myelin regulatory factor (MYRF), which impairs its ability to interact with the MBP promoter (Huang et al., 2015). Indeed, in a recent study disrupted myelination of corpus callosum axons by engrafted human oligodendroglial cells expressing mHTT was rescued by co-expressing SOX10 and MYRF demonstrating the important role this transcription factor plays in myelination related deficits in HD (Osipovitch et al., 2019). Strikingly, transcriptional dysregulation in human oligodendrocytes expressing mHTT is also observed in the common progenitor of both astrocytes and oligodendrocytes as well as at earlier stages of neural development, when stem cells become committed to this lineage, suggesting that the dysfunctional biology and development of both of these cell types could be encoded at a relatively early stage (Haremaki et al., 2019; Osipovitch et al., 2019; Ruzo et al., 2018).

Importantly, mice expressing mHTT specifically in the oligodendroglial lineage also have significantly reduced body weight and similar impairments in motor phenotypes to those seen in HD model mice that express mHTT in every cell. Also, as observed in other HD models, these mice have an increased propensity to undergo seizures in response to flurothyl treatment and have a reduced lifespan (Huang et al., 2015). While these results demonstrate that mHTT expression in oligodendrocytes is sufficient to induce pathology, care should be taken in concluding what this data tells us about the ways in which oligodendrocytes are affected by and contribute to HD pathogenesis. In this study, the more toxic N terminal fragment, rather than the

full-length mHTT gene, was expressed under the control of the strong PLP promoter, leading to significant aggregation of mHTT protein in these cells, a phenotype that is not observed in global knock-in mouse models of the disease. It will be interesting to see if similar phenotypes are replicated when the full-length *mHTT* gene is driven under its endogenous promoter, perhaps using a *Cre*-based lox-stop-lox approach.

In addition to the cell-autonomous pathological actions of mHTT expression in oligodendroglial cells, the selective inactivation of mHTT in chondroitin sulfate proteoglycan NG2 (NG2) expressing oligodendrocyte progenitors is sufficient to prevent myelin abnormalities and rescue certain behavioral deficits in HD mice. Using *Ng2-Cre* to genetically ablate *mHTT* in the BACHD model, Bardile and colleagues completely restored both the thickness of myelin sheaths and their level of compaction. This was accompanied by increased expression of myelin proteins including ermin, MBP, MAG, and septin-8. At least some of this rescue could be explained by reduced activity of the polycomb repressive complex 2 (PRC2), an important epigenetic regulator that is activated by mHTT in a polyglutamine length–dependent manner (Ferrari Bardile et al., 2019).

While the ablation of mHTT in oligodendrocyte precursors is not sufficient to rescue the forebrain atrophy and striatal volume loss seen in BACHD mice, it does rescue some behavioral phenotypes. Climbing performance is improved at both 2 and 6 months of age, although no improvements were seen at later time points. In addition, depressive-like phenotypes assessed with the Porsolt forced swim test (FST) are also improved following oligodendroglial mHTT ablation (Ferrari Bardile et al., 2019).

Taken together, these results demonstrate the important role mHTT expression in oligodendrocytes plays in HD pathogenesis and suggest that targeting cell-intrinsic mechanisms underlying myelination deficits could potentially have beneficial therapeutic effects.

<u>Changes in myelin properties occur in pre-symptomatic HD patients</u>

In both pre-symptomatic and manifest HD patients, T1-weighted diffusion tensor imaging (DTI) (which measures the magnitude and direction of water diffusion through the tissue) has identified micro-structural changes in the properties of myelin that are indicative of damage (Di Paola et al., 2012; Di Paola et al., 2014; Dumas et al., 2012; Kloppel et al., 2008; Matsui et al., 2014; Matsui et al., 2015; Novak et al., 2014; Phillips et al., 2013; Phillips et al., 2014; Phillips et al., 2016; Poudel et al., 2015; Rosas et al., 2010; Steventon et al., 2016). Measures of white matter organization (fractional anisotropy) and myelin integrity (radial diffusivity) are changed in the corpus callosum, sensori-motor pathway, cortico-spinal tract, and superficial white matter areas of the cortex in pre-symptomatic HD patients in both a spatially selective and temporally

predictable manner that reflects myelin damage (Bohanna et al., 2011; Di Paola et al., 2012; Dumas et al., 2012; Novak et al., 2014; Phillips et al., 2013; Phillips et al., 2016; Rosas et al., 2010). These changes also correlate with observed declines in a number of different clinical metrics of motor and cognitive function, including unified Huntington's disease rating scale (UHDRS) score and mini-mental state exam (MMSE) score, as well as individual measures of motor and cognitive function including the symbol digit, verbal fluency, and Stroop color word tests (Bohanna et al., 2011; Di Paola et al., 2012; Dumas et al., 2012; Gregory et al., 2015; Phillips et al., 2013; Rosas et al., 2010). Importantly, longitudinal studies in which myelin properties are monitored in the same individuals over an 18-month period also find similar declines in myelin but not axonal micro-structure in pre-symptomatic HD patients (Poudel et al., 2015).

In addition to impairments in myelin microstructure, iron levels in deep white matter structures change in HD patients. Di Paola et al. observed a global increase in iron levels in deep white matter tracts in the pre-symptomatic phase of the disease, followed by a reduction in levels at symptom onset (Phillips et al., 2014). While the biological significance of this is still unclear, oligodendrocytes have a high iron content relative to other brain cell types, and iron plays important roles in myelination as well as in many other cellular processes including acting as a cofactor for a number of different enzymes, functioning in ATP production, and participating in the synthesis of DNA, ribonucleic acid (RNA), and proteins (Reinert et al., 2019; Todorich et al., 2009). It is thought that the initial increase in iron levels might be caused by a proliferation of oligodendrocyte precursors as a compensatory response to myelin damage, a finding that is supported by post-mortem studies demonstrating an increase in oligodendrocyte numbers in tissue from pre-symptomatic HD patients (Gomez-Tortosa et al., 2001). Similarly, the reduction of iron levels at later stages could reflect a failure of oligodendrocytes to respond to ongoing damage, accompanied by an increase in cell and tissue loss. However, further studies would need to confirm this.

Pericytes

Pericytes are associated with capillary cell walls and act at many levels to control vascular functions within the CNS (Brown et al., 2019; Cheng et al., 2018; Sweeney et al., 2016). Through their regulation of the endothelial cell cycle and the secretion of angiogenic-promoting factors, they promote vascular development and angiogenesis (Bergers and Song, 2005; Payne et al., 2019; Ribatti et al., 2011; Wang et al., 2014b; Zaitoun et al., 2019). They also respond to changes in neuronal activity to constrict or relax around capillaries and thus regulate cerebral blood flow (Cai et al., 2018; Hall et al., 2014; Mishra et al., 2016). In addition, they modulate and

maintain the blood brain barrier through the release of signaling factors, which determine the number of endothelial cell tight junctions and direct the polarization of astrocyte end feet (Armulik et al., 2010; Bell et al., 2010; Daneman et al., 2010; Ma et al., 2018; Sengillo et al., 2013). Alongside their vascular roles, pericytes regulate immune cell entry into the brain at least in part through their crosstalk with endothelial cells and have stem cell–like properties with the capacity to differentiate into a variety of other cell types (Bell et al., 2012; Dore-Duffy et al., 2006; Nakagomi et al., 2015; Ozen et al., 2014; Rustenhoven et al., 2017; Wang et al., 2006).

The ways in which pericytes contribute to and are affected by Huntington's disease pathology have not been extensively studied. However, a recent investigation has suggested that vascular abnormalities in the striatum are accompanied by a change in the number and biology of pericytes. Padel and colleagues found that, in the R6/2 HD model, the number of platelet-derived growth factor receptor beta (PDGFRβ)-positive pericytes is increased at 12 weeks of age, prior to changes in body weight and some aspects of motor performance (Table 2). This is accompanied by a change in local vascular properties in the striatum including an increased amount of platelet endothelial cell adhesion molecule (CD31) positive blood vessel branching and an increased proportion of smaller blood vessels (Padel et al., 2018). In addition, a higher proportion of pericytes express proteins that reflect their engagement in vascular remodeling such as regulator of G protein signaling 5 (RGS5) and NG2 (Ozen et al., 2014; Padel et al., 2018). While it remains to be determined if pericyte activation in HD precedes and drives vascular changes, the temporal correlation of these events is intriguing. Importantly, the authors show that some phenotypic changes in pericytes can also be observed in human disease, such as an increased number of PDGFRβ and NG2 expressing pericytes present in post-mortem HD tissue with a high pathological grade (Padel et al., 2018). Given the diverse array of functions pericytes perform in the healthy brain, future studies exploring the role of this cell type in HD, perhaps using genetic strategies to deplete or alter their functions during disease-relevant windows, will be important.

Insights from Drosophila models

In addition to the vertebrate models discussed above, new insights have been gained by studying genetically tractable drosophila HD models. Drosophila share with vertebrates molecular mechanisms related to body axes patterning, nervous system wiring, organogenesis, and cell proliferation (Acampora et al., 1998; Arendt and Nubler-Jung, 1999; Cheesman et al., 2004; Hartmann et al., 2000; Holley et al., 1995; Kasture et al., 2018; Leuzinger et al., 1998; McDonald et al., 1998; Reichert, 2009; Rosas-Arellano et al., 2018; Weiss et al., 1998). They are capable of reproducing the cellular, morphological, physiological, and behavioral

impairments observed in a variety of neurodegenerative diseases (Chakraborty et al., 2011; Elia et al., 1999; Greene et al., 2003; Mhatre et al., 2014; Nishimura et al., 2010; Stempfle et al., 2010; Stokin et al., 2008; Watson et al., 2008). Over the last 20 years, a variety of drosophila HD models have been generated and used to study everything from structural biology related to mHTT cleavage and aggregation to the transcriptional and behavioral impacts of its effects on metabolic imbalance, protein trafficking, and autophagy (Babcock and Ganetzky, 2015; El-Daher et al., 2015; Ravikumar et al., 2008; Weiss et al., 2012; Weiss and Littleton, 2016; Zala et al., 2013; Zhang et al., 2010).

The existence of genetic tools that enable mHTT expression to be driven only in specific cellular populations combined with the ability to use drosophila models to rapidly screen for genetic modifiers of pathology has provided some key insights. Using the UAS-GAL4 system to drive expression of mHTT in specific glial populations, Lievens and colleagues found that expression of mHTT either in surface glia, which cover the central nervous system and help to maintain the blood brain barrier, or peripheral glia, which ensheath axons and are the fly homologue of the mammalian Schwann cell, has no effect on motor performance or life expectancy. In contrast, driving expression of mHTT in cortical glia, which modulate synaptic neurotransmission and share many properties with vertebrate astrocytes, is sufficient to induce early lethality. However, it is only when mHTT expression is driven by a pan glial driver that other HD phenotypes, such as motor deficits, start to appear (a finding that has also been replicated in other studies) (Lievens et al., 2008; Tamura et al., 2009). This could result from either the combined pathological effect of mHTT expression in multiple glial cell types or the expression of mHTT in other glial populations that have not yet been interrogated.

Studies have also found that expression of the mutant gene under a pan glial driver negatively impacts both the blood brain barrier and the blood retina barrier, phenotypes that have not yet been extensively explored in the context of glia-mediated pathology in vertebrate models. Driving mHTT in glial populations that exist at these barriers makes them more porous to specific dyes and impacts the electrophysiological properties of photoreceptor transmission (Yeh et al., 2018).

Investigators have also tested whether glia mediated HD pathology can be alleviated by induced expression of genes previously identified in genetic modifier screens. It was found that protein kinase B alpha (AKT), which offers protection against apoptotic stimuli, rescues motor phenotypes but not reductions in lifespan (Lievens et al., 2008). In contrast, overexpressing molecular chaperone heat shock protein 70 delays early lethality, rescues the expression of glial glutamate transporter dEAAT1, and restores BRB/BBB function (Yeh et al., 2018). In addition,

overexpression of both a mitochondrial uncoupling protein (UCP), which regulates proton translocation and thus determines the way in which energy is supplied in the cell, and a glucose transporter is sufficient to rescue both motor and early lethality phenotypes. Interestingly, this rescue effect is not observed when mHTT expression is driven in neuronal populations, suggesting either diversity in the pathology induced by the cell-autonomous actions of mHTT in these two cell types or a different contribution of this gene to the normal functioning of these cells (Besson et al., 2010).

Conclusions and outlook

Glial cells are both affected by and contribute to aspects of Huntington's disease pathology. While in some cases, glial cell dysfunction is characterized by a disruption of normal biological roles, such as the impaired myelination attributed to changes in oligodendrocyte biology, there are also reactive changes, such as the increased expression of inflammatory cytokines by microglia (Crotti et al., 2014; Garcia-Miralles et al., 2019; Jin et al., 2015). Given the nascent state of glial research in Huntington's disease and neurodegenerative diseases more broadly, more evidence is needed to address whether glia act as drivers of pathogenesis in HD. However, given the cell-autonomous pathology generated by selective expression of mHTT in specific glia and the evidence that glial dysfunction occurs very early in HD pathogenesis, it is very unlikely that they are simply responding to neuronal damage (Bohanna et al., 2011; Bradford et al., 2009; Crotti et al., 2014; Di Paola et al., 2012; Dumas et al., 2012; Huang et al., 2015; Jin et al., 2015; Novak et al., 2014; Pavese et al., 2006; Phillips et al., 2013; Phillips et al., 2016; Politis et al., 2015; Politis et al., 2011; Rosas et al., 2010; Tai et al., 2007; Tong et al., 2014). Instead, their involvement in HD pathology is probably defined by a combination of intrinsic dysfunction and their responses to disease-induced changes in their local micro-environment. New tools and approaches to manipulate and track specific glial populations, perhaps using novel cre drivers that more specifically label different types and states of glial cells as well as in vivo imaging tools that enable changes in molecular signaling to be assessed, are needed to address whether and how glia impact different aspects of HD progression and pathobiology.

Understanding normal biology can provide important new insights into disease mechanisms. Here we outlined many aspects of glial dysfunction in Huntington's disease, but surprisingly, many of the known functions of astrocytes, microglia, oligodendrocytes, and pericytes remain unexplored in the context of HD pathogenesis. This is particularly true for pericytes, where the cell-autonomous functions of mHTT have yet to be interrogated, and microglial cells, which have traditionally been examined in terms of their expression of

inflammatory cytokines. A growing body of evidence has shown that microglia play a role in a large number of processes in the healthy and developing brain, including neurogenesis, axonal pruning, the maturation and myelination of oligodendrocytes, and synaptic refinement, and these deserve to be explored in the context of HD (Akiyoshi et al., 2018; Cunningham et al., 2013; Filipello et al., 2018; Hagemeyer et al., 2017; Hammond et al., 2018; Pang et al., 2013; Paolicelli et al., 2011; Ribeiro Xavier et al., 2015; Schafer et al., 2012; Squarzoni et al., 2014; Weinhard et al., 2018; Wlodarczyk et al., 2017; Zhan et al., 2014).

One class of brain glial cells, the ependymal cells, which include ependymocytes, choroid plexus epithelial cells, tanocytes, and retinal muller and pigment epithelial cells, have not been examined at all in the context of HD. These cells line the central canal and ventricular cavities of the CNS and form an interface between the cerebrospinal fluid, brain, and spinal cord parenchyma. They have been suggested to play a role in a variety of processes in the developing brain, including neurogenesis, neuronal differentiation, and axonal guidance, and in the adult, they have important secretary roles expressing both immunomodulatory agents, such as cytokines, as well as growth factors to promote repair following injury (Bruni, 1998; Gajera et al., 2010; Hoffman et al., 2007; Moore, 2016; Moore and Oglesbee, 2012; Ramirez-Castillejo et al., 2006; Shah et al., 2018; Sugama et al., 2002; Tarlow et al., 1993). Given these important roles in the healthy brain and their reactive response to injury paradigms, these cells should also be examined in the context of HD pathogenesis.

Moving forward, it will also be important to consider whether the structural and transcriptional heterogeneity of glial cell populations, which have recently been demonstrated with ground-breaking single-cell profiling technologies, play a role in their response to and involvement in HD pathogenesis (Buosi et al., 2018; Chai et al., 2017; Emsley and Macklis, 2006; Hammond et al., 2018; Lawson et al., 1990; Li et al., 2019; Marques et al., 2018; Marques et al., 2016; Martin et al., 2015; Oe et al., 2016). However, before this can take place, new tools will be required to translate these transcriptional states into functional roles that can be interrogated. In addition, while some studies have already attempted to determine the significance of mHTT-induced glial dysfunction on HD pathogenesis by investigating changes in neuronal physiology, future investigations should expand on this to look at the ways in which altered glial biology impacts neuronal circuits and networks. This will not only provide greater insight into behaviors that might be altered in the disease but also will be important more generally in determining how glial cells integrate into and regulate these processes.

Glial cell crosstalk should also be considered when examining the dysfunction of specific cell types in HD, for example, microglia prompt changes in the transcriptional and

functional profile of astrocytes in certain contexts, so strategies that take this into account when examining cell-autonomous dysfunction caused by mHTT expression should be implemented (Liddelow et al., 2017). While the complexity of the brain microenvironment makes identifying cell type–specific communication a challenge, one strategy to overcome this would be to generate more complex, multicellular culture systems that maintain the physiological behavior of glial cells but are more tractable with regards to genetic and pharmacological intervention .

The rescue of various aspects of HD pathology alongside improvements in motor and cognitive performance that have been achieved by specifically eliminating mHTT expression in different glial cell populations or restoring their normal biological functions with targeted viral approaches offer the tantalizing prospect of glia-targeted therapies for HD. These are, however, still some way in the future. Hopefully, the advent of new tools to manipulate glial cell biology in both the healthy and diseased brain alongside genetic, transcriptomic, and imaging studies will enable greater insight into the complexities of glial cell biology and its dysfunction in HD and identify new targets for therapeutic intervention. This is an exciting time for glial research in HD and neurodegenerative diseases more broadly, with many important unanswered questions about the way in which these cells might be affected by as well as drive different aspects of pathology at different stages of the disease. The rapid rise of transcriptional profiling technologies as well as the development of new ways to interrogate physiological functions and brain circuits will hopefully enable rapid progression in this key area of biological research.

Disclosure statement

B.S. serves on the scientific advisory board of Annexon Biosciences and is a minor shareholder of this company.

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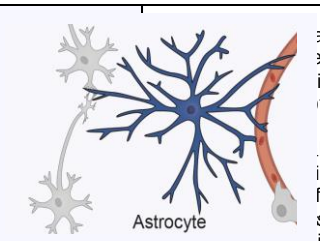
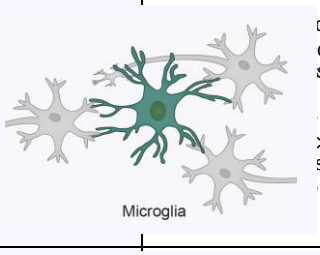
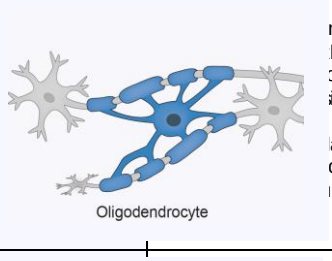
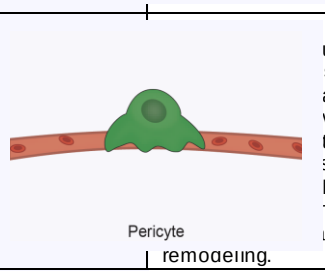
Table 1

Glial cell dysfunctions in Huntington's Disease

Abbreviations: Kir4.1, ATP-sensitive Inward Rectifier Potassium Channel 10; GLT-1, Glutamate transporter 1; NMDAR, N-methyl-D-aspartate receptor; PU.1, Spleen Focus Forming Virus (SFFV) Proviral Integration Oncogene; C/EPB, CCAAT Enhancer Binding Protein Beta; mHTT, Mutant Huntingtin; HD, Huntington's disease; MYRF, Myelin Regulatory Factor; PDGFRβ, Platelet Derived Growth Factor Receptor Beta; RGS5, Regulator Of G Protein Signaling 5; NG2, Chondroitin Sulfate Proteoglycan NG2. References: For astrocytes - Octeau et al., 2018, Diaz-Castro et al., 2019, Tong et al., 2014, Jiang et al., 2016, Skotte et al., 2018, Valenza et al., 2015, Bradford et al., 2009, Wood et al., 2019, Arzberger et al., 1997, Hodges et al., 2006, Faideau et al., 2010, Liddelow et al., 2017. For microglia – Franciosi et al., 2012, Simmons et al., 2017, Sapp et al., 2001, Kwan et al., 2012b, Kwan et al., 2012a, Pido-Lopez et al., 2018, Crotti et al., 2014, Silvestroni et al., 2009, Bjorkqvist et al., 2008, Petkau et al., 2019. For oligodendrocytes – Garcia-Miralles et al., 2019, Jin et al., 2015, Teo et al., 2016, Ferrari Bardile et al., 2019, Huang et al., 2015, Teo et al., 2019, Bohanna et al., 2011, Di Paola et al., 2012, Dumas et al., 2012, Novak et al., 2014, Phillips et al., 2013, Phillips et al., 2016, Rosas et al., 2010. For pericytes – Padel et al., 2018

	Glial cell dysfunctions observed in animal models of HD	Changes observed in human disease	Cell autonomous dysfunction elicited by mHTT expression in this cell type	HD pathologies and behaviors rescued by *mHTT* ablation/reduction from this cell type

 ation of es with inputs. tional l in part by f Kir 4.1. sion of neuronal metabolites.	- Reduced expression of *Kir4.1* and *GLT-1* which drive some of the altered electrical properties in mouse HD models. - Evidence of astrogliosis, which has also been observed in multiple mouse HD models.	- Reduced expression of GLT-1. - Impaired motor performance. - Reduced body weight. - Lower life expectancy.	- Slower decline in motor performance. - Partial abrogation of depressive behavioral phenotypes. - Increased striatal volume. - Normalization of evoked NMDAR currents in medium spiny neurons.
 ore ogy. s to cues. ssion of kines.	- Adoption of a more ameboid morphology. - Increased expression of inflammatory cytokines.	- Increased expression of inflammatory cytokines driven by the actions of PU.1 and C/EPB transcription factors. - Generation of a neurotoxic environment following sterile inflammation	- Reduced expression of inflammatory cytokines when mHTT expression is lowered in microglia. - No rescue of motor performance following mHTT lowering in microglia. - No rescue of brain volume reductions following mHTT lowering in microglia.
 nner h on. ion of ation of ollowing lt.	- Impaired myelin micro-structure in pre-symptomatic HD patients. - Increased iron levels in the deep white matter of presymtomatic HD patients which decline in the manifest phase of the disease.	- Thinner myelin sheaths. - Reduced expression of myelin proteins due to sequestration of transcription factor MYRF. - Reduced body weight. - Impairments in motor phenotypes. - Increased propensity of mice to undergo seizures.	- Restoration of myelin sheath thickness and compaction. - Increased expression of myelin proteins. - Improved climbing performance. - Improved performance in the Porsolft forced swim test which assesses depressive phenotype.
 umbers ssing anied by vascular triatum. ssion of hich are n scular remodeling.	- Increased number of PDGFRβ and NG2 expressing pericytes.	- Unknown	- Unknown

HD model	HD gene characteristics	Key pathological/neuropathological hallmarks and age of onset	Behavioral abnormalities and age of onset	Glial cell
R6/2	- Transgene expressing exon 1 of human mHTT. - Expression is driven by the HD promoter. - Multiple strains exist with various CAG (Q) repeat lengths however the 120Q line is widely used.	- mHTT aggregates can be detected at 4 weeks of age. - Brain atrophy can be detected at 6 weeks of age. - Body weight reductions noted from 8 weeks of age. - Median live span is 16 weeks.	- Cognitive deficits at 3.5 weeks of age comprising spatial and non- spatial learning and memory deficits. - Motor deficits at 4 weeks of age comprising impaired rotarod performance, abnormal gait, hind paw clasping and impaired grip strength.	**Astrocytes** - Territory cover significantly red - Striatal astrocy cortical inputs a - Striatal astrocy profiles at 8 we - Striatal astrocy levels and at 10 impaired K^+ hor - Striatal astrocy levels at 10 wee - Striatal astrocy spontaneous ar weeks of age. - Processing of

				is impaired at 1 **Microglia** - Striatal microg and density at 3 - Striatal microg inflammatory cy **Pericytes** - The number o increased at 12 accompanied b involved in vasc
BACHD	- Transgene expressing full length human mHTT with exon 1 floxed. - Expression is driven by the HD promoter.	- mHTT aggregates can be detected at 12 months of age. - Striatal and brain atrophy have been documented at 12 months of age. - Body weight gain at 12 weeks. - Median live span is not significantly different to WT littermates.	- Motor deficits at 2 months of age comprising impaired rotarod, open field and climbing performance. - Increased anxiety detected in the light/dark choice test at 2 months of age. - Depression like phenotypes detected with the forced swim test at 2 months of age.	**Microglia** - Microglia isola increased expre - Microglia show well as in respo months
YAC128	- Transgene expressing full length human mHTT. - Expression is driven by the HD promoter	-mHTT aggregates can be detected at 12 months of age. -Striatal and brain atrophy have been documented at 12 months of age. -Body weight gain at 12 weeks. -Median live span is not significantly different to WT littermates.	- Motor deficits at 2 months of age comprising: impaired rotarod performance. - Depression like phenotypes detected with the forced swim test at 12 months.	**Microglia** - Striatal microg but not density **Oligodendrocy** - Thinner myelin callosum at 1.5 - Mature oligode for myelin prote age.
zQ175 KI	- Knock-in of expanded CAG repeat into endogenous murine HTT gene, chimeric human/mouse exon 1 inserted.	- mHTT aggregates can be detected at 2 months of age. - Brain atrophy can be detected at 12 months of age. - Body weight loss at 8 weeks of age. - For homozygotes median live span is 20 weeks.	- Motor deficits at 7 months of age comprising: impaired rotarod, open field and climbing performance. - Impaired performance in visual discrimination tasks at 6 months of age and in the procedural two choice swim cognitive test at 10 months of age.	**Astrocytes** - Striatal astrocy display lower m months of age (- Striatal astrocy profiles at 6 mo - Striatal astrocy GLT-1 at 10 mo **Microglia** - Striatal microg profile at 18-20 - Striatal microg inflammatory cy

Table 2

Commonly used HD mouse models in which assessments of glial cell dysfunction are available

*It should be noted that the time points referenced above do not necessarily reflect the earliest occurrence of the cellular, pathological or behavioral phenotype being described in these models. These are merely the time points chosen by the authors of these studies. In almost all cases further investigation would be required to determine when these abnormalities arise.

**It should also be noted that just because dysfunction of a particular glial cell type or a particular type of dysfunction related to that cell is not mentioned for some mouse models of HD it does not mean that it doesn't occur. Many phenotypes have only been studied in only one or possibly two HD models. The choice of these models is at the discretion of the authors and their rationale for selecting them is often not articulated.

Abbreviations: Kir4.1, ATP-sensitive Inward Rectifier Potassium Channel 10; GLT-1, Glutamate transporter 1; mHTT, Mutant Huntingtin; HD, Huntington's disease;

References: A field Guide to Working with Mouse Models of Huntington's Disase: Menalled et al, Octeau et al., 2018, Diaz-Castro et al., 2019, Tong et al., 2014, Jiang et al., 2016, Skotte et al., 2018, Valenza et al., 2015, Franciosi et al., 2012, Kwan et al., 2012b, Kwan et al., 2012a, Pido-Lopez et al., 2018, Crotti et al., 2014, Petkau et al., 2019, Savage et al., 2020, Garcia-Miralles et al., 2019, Jin et al., 2015, Teo et al., 2016, Ferrari Bardile et al., 2019, Teo et al., 2019, Padel et al., 2018, Curtin et al., 2015, Gray et al., 2008, Menalled et al., 2012, Heikkinen et al., 2012