

Neuroinflammation in Huntington's disease

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Abstract Huntington's disease (HD) is a monogenic neurodegenerative disease characterized by abnormal motor movements, personality changes and early death. In contrast to other neurodegenerative diseases, very little is known about the role of neuroinflammation in HD. While the current data clearly demonstrate the existence of inflammatory processes in HD pathophysiology, the question of whether neuroinflammation is purely reactive or might actively participate in disease pathogenesis is currently a matter of ongoing research and debate. This review will try to shed some light on the current state of research in this area and provide an outlook on potential future developments.

Keywords Neuroinflammation · Microglia · Huntington's disease · Non-cell autonomous · Neurodegenerative disease · Glia

Microglia and neuroinflammation

There are several recent reviews on the cell biology of microglia and their role in neuroinflammation (e.g. Garden and Möller 2006; Hanisch and Kettenmann 2007; Ransohoff and Perry 2009). The interested reader is referred to those for more background information on this topic. The following brief introduction is given to facilitate the better understanding of microglial cells for the reader whose main focus is neurodegenerative disease.

Microglia are the resident immune cells of the CNS. They resemble peripheral tissue macrophages and are the primary mediators of neuroinflammation (van Rossum and Hanisch 2004; Ransohoff and Perry 2009). Studies in the last two decades have demonstrated the involvement of microglia in many acute and chronic neurological diseases (Hanisch and Kettenmann 2007; Sugama et al. 2009). In the healthy adult brain, microglia exist as so-called "resting" or "surveilling" microglia, characterized by a small cell body with fine, ramified processes and minimal expression of surface antigens. Upon CNS injury, these cells are rapidly activated, transform to a less ramified morphology and participate in the pathogenesis of neurological disorders. They secrete various inflammatory molecules, including TNF- α , IL-6 and nitric oxide (Hanisch et al. 2002). When CNS cells die, microglia are further activated and become phagocytes. It is widely believed that substances released from damaged cells within the brain trigger microglial activation, consequently leading to the long-term changes of gene expression and reorganization of the cell (van Rossum and Hanisch 2004; Hanisch and Kettenmann 2007). Activated microglia exert their effects on neurons and macroglia (astrocytes and oligodendrocytes) through the release of cytotoxic substances such as oxygen radicals, nitric oxide, glutamate, proteases, and neurotoxic cytokines, as well as cytoprotective agents such as growth factors, plasminogen, and neuroprotective cytokines (van Rossum and Hanisch 2004). The effects of microglia are themselves modulated by astrocytes and neurons through cytokines and neurotransmitters, thus giving rise to complex interactions between microglia, neurons and astrocytes. This intricate dance is commonly called "neuroinflammation". While there might be as many interpretations of neuroinflammation as there are articles in this special issue, an important distinction should be made for the purpose of this review. In acute or infectious settings

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such as stroke, HIV encephalopathy or the prototypic neuroinflammatory disease multiple sclerosis, neuroinflammation is propagated by CNS intrinsic cells such as microglia and astrocytes as well as infiltrating peripheral immune cells such as monocytes and T-cells (Carson 2002; Garden 2002; Weinstein et al. 2010). In contrast, the evidence that peripheral immune cells play a significant role in the pathogenesis of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) is still sparse and debated (Streit 2005; Weydt and Möller 2005; Kim and Joh 2006; Appel et al. 2010, and as reviewed in other sections of this special issue.)

Huntington's disease

Huntington's disease (HD) is a progressive, autosomal-dominant neurodegenerative disease. It is characterized by abnormal motor movements, including chorea and dystonia, cognitive decline, personality changes and early death (Vonsattel and DiFiglia 1998; Walker 2007). Typical onset is between 35 and 45 years of age, but onsets from 2 to 85 years of age have been reported. Patients usually die 10–15 years after onset of symptoms due to bulbar dysfunction and complications. Neuropathologically, HD is characterized by severe atrophy of the caudate and putamen (Vonsattel et al. 1985; Vonsattel and DiFiglia 1998). Striatal medium-sized spiny neurons containing the neurotransmitter GABA are the most vulnerable neuron population. Degeneration of the globus pallidus occurs secondary to the loss of striatopallidal projection fibers and cerebral cortical atrophy is common. In contrast, cerebellar Purkinje cells are spared, except in juvenile onset cases (Vonsattel and DiFiglia 1998).

Linkage analysis led to the discovery of *IT-15*, the gene the causative mutation underlying HD (HDCR Group 1993). It contains an unstable CAG trinucleotide repeat expansion, which is translated into a polyglutamine (polyQ) stretch within the huntingtin (htt) protein (Li and Li 2004; Cattaneo et al. 2005; Gusella and Macdonald 2006). Similar abnormal CAG expansions occur in at least seven unrelated genes, all associated with neurodegenerative disease (Orr and Zoghbi 2007). In HD the expression of 35 or more glutamines in htt (htt^{exp}) causes disease and the age of onset is inversely related to the length of the CAG repeat (Andrew et al. 1993; Snell et al. 1993). While the exact mechanisms by which the expanded polyQ stretch causes disease are still unknown, there is a positive correlation between repeat length and increased aggregation kinetics (Walker 2007).

Htt is a 348 kDa protein with no immediately obvious function. It contains multiple HEAT repeats, hydrophobic

α -helices that mediate protein–protein interactions, suggesting that htt is a multifunctional scaffolding protein (Andrade and Bork 1995). Indeed, yeast two-hybrid screens have revealed a large number of proteins (>180) that directly interact with htt (Goehler et al. 2004; Li and Li 2004). Htt is ubiquitously expressed, is essential for embryogenesis and, despite its size, completely soluble. (Li and Li 2004; Cattaneo et al. 2005; Gusella and Macdonald 2006). Based on dominant inheritance and the observation that absence of htt leads to embryonic lethality rather than late onset neurodegenerative disease, the polyQ stretch is believed to confer a toxic gain-of-function (Gusella and MacDonald 2000), however a loss-of-function mechanism may contribute to late stage disease (Cattaneo et al. 2001).

Several mechanisms have been implicated in HD pathogenesis, including: (1) disruption of axonal transport; (2) excitotoxicity via NMDA receptors; (3) htt^{exp}-mediated cytoplasmic sequestration of transcription factors and (4) mitochondrial/bioenergetic dysfunction (Li and Li 2004; Orr and Zoghbi 2007; Imarisio et al. 2008; Roze et al. 2008). None of them are mutually exclusive and most likely a combination of processes lead to the pathology observed in HD.

The identification of htt^{exp} as the underlying genetic cause has enabled the HD community to generate several genetic animal models of HD, which have now widely replaced phenotypic models (Beal and Ferrante 2004; Hersch and Ferrante 2004; Ferrante 2009; Gil and Rego 2009). The genetic mouse models fall broadly into three categories: (1) transgenic mice which express exon 1 fragments of the human htt with disease causing CAG repeat stretches, e.g. R6/2 mice, the most extensively characterized HD mouse model so far (Mangiarini et al. 1996); (2) knock-in mice with pathogenic CAG repeats inserted into the murine huntingtin (Hdh), e.g. the Hdh^{Q150/Q150} mice (Lin et al. 2001); and (3) mice that express the full length human HD gene from a YAC or BAC, e.g. the YAC128 mice (Slow et al. 2003). Virtually all of these mice develop motor symptoms (albeit to extremely varying degrees), show transcriptional abnormalities and show htt^{exp} inclusions. While the different mouse models have their inherent advantages and disadvantages, they all have been instrumental in our understanding of HD pathogenesis and are an extremely valuable tool for the research on experimental therapeutics (Beal and Ferrante 2004; Hersch and Ferrante 2004; Ferrante 2009; Gil and Rego 2009).

Although htt^{exp} was identified as the initial trigger for HD, the cellular mechanisms leading to pathology remain enigmatic. Recent data has also challenged the idea that HD is a purely neuronal cell-autonomous disease, i.e. only neuronal htt^{exp} is causing the disease. Indeed, htt is expressed widely in neurons and glial cells (Li et al. 1993;

Buraczynska et al. 1995; Trotter et al. 1995). However the role of non-neuronal htt^{exp} in pathogenesis has only been investigated recently. Htt^{exp} accumulates in glial nuclei in HD brains and reduces the expression of glutamate transporters (Shin et al. 2005). Furthermore, mice with htt^{exp} expression restricted to selected neuronal populations have considerably reduced motor deficits and striatal neuropathology (Gu et al. 2005, 2007). In contrast, transgenic expression of htt^{exp} in astrocytes alone leads to HD-like symptoms or worsens disease progression when crossed into existing HD models (Bradford et al. 2009, 2010). Such studies show that cell–cell interactions are necessary for striatal pathogenesis and suggest a two-hit hypothesis where both cell-autonomous toxicity and cell–cell interactions are critical in HD pathogenesis (Gu et al. 2007).

Microglia and HD

Although microglial cells are implicated in nearly all disorders of the CNS, the role of microglia in HD is just beginning to be explored. The first report of microglial abnormalities were described by Singhrao et al. (1999) in a report about complement activation in human HD. Microglial cell counts were considerably increased in the caudate putamen of HD and these microglial cells expressed increased amounts of complement factors (see below). A more detailed investigation of microglial morphological changes associated with HD was performed by Sapp et al. (2001). The authors localized morphologically activated microglial cells in the neostriatum, cortex and globus pallidus as well as in adjoining white matter of HD brains. In the striatum and cortex the accumulation of thymosin β -4 reactive microglia increased with grades of pathology (Vonsattel grades 1–4) and grew in density with in relation to the degree of neuronal loss. In a subsequent report microglial accumulation was observed in HD tissue, as well as in the striatum R6/2 mouse model (Simmons et al. 2007). This study was also the first to show via immunohistochemistry that microglial cells indeed express htt^{exp}, which in some cells also formed aggregates. This is noteworthy, as aggregated htt^{exp} has been reported to lead to transcriptional changes in neurons (Cha 2007; Kuhn et al. 2007) and it is therefore likely that microglial transcription might be influenced in a similar manner.

PET studies showing microglial activation in HD

Recent progress in imaging technology has provided for a method to non-invasively monitor neuroinflammatory changes in human disease (Cagnin et al. 2007). A ligand for the peripheral benzodiazepine receptor (PBR), PK-11195,

labels activated microglia [and to a lesser extent astrocytes (Hertz et al. 2006)] and can be used to pinpoint areas of increased glial activation. Initial studies showed that microglial activation in HD patients correlates with disease progression as assessed by loss of dopamine D2 receptor binding sites (Pavese et al. 2006; Tai et al. 2007a). Most notably, a follow up publication showed that microglial activation is also evident in presymptomatic HD gene carriers and can be detected up to 15 years before predicted age of onset (Tai et al. 2007b). Intriguingly, a higher level of microglia activation already correlated with a lower level of dopamine D2 receptor binding sites and was associated with a higher probability of developing HD in 5 years. These findings indicate the microglial activation is an early event associated with subclinical progression of HD.

Microglial ferritin accumulation

In a recent report microglial ferritin accumulation was observed in HD tissue as well as in the R6/2 mouse model (Simmons et al. 2007). Ferritin accumulation in striatal microglia is an early event in HD mice (2–4 weeks) and increased with disease progression in mice as well as with neuropathological grades (Vonsattel grades) in humans. Interestingly, the increase of iron in HD brains has been known for almost 20 years (Dexter et al. 1991). More recent data has shown that htt is an iron-regulated protein (Hilditch-Maguire et al. 2000). Htt^{exp} inclusions are iron dependent centers of oxidative stress (Firdaus et al. 2006), which is one of the proposed mechanisms of neuronal injury in HD (Shoham and Youdim 2000). Iron is also an important regulator of immune cell function (Theurl et al. 2005). While there is ample data on iron regulation and effects in peripheral macrophages, very little is known about microglial iron handling (Zhang et al. 2006). It is currently unclear if the increase in ferritin is a reaction to extracellular signals or caused by htt^{exp} in microglial cell themselves. Furthermore it is not known what the functional consequence of this ferritin increase is. Is it a protective response to reduce the potentially detrimental free iron pool and thereby reducing oxidative stress or is it depleting necessary iron by sequestering it? Intriguingly, a mutation in the light chain of ferritin causes adult-onset basal ganglia disease with extrapyramidal features similar to HD (Curtis et al. 2001).

Complement

The complement system is part of the innate immune system and provides powerful cytotoxic and cytolytic activities against a large variety of pathogens (Carroll

2004). While long ignored in neuroscience research as a peripheral component of the innate immune system, it has become increasingly clear that complement is synthesized in the CNS and participates in most CNS pathologies from acute stroke to chronic neurodegenerative diseases such as AD or HD (Hauwel et al. 2005; Bonifati and Kishore 2007; Griffiths et al. 2009). In the HD striatum, neurons, astrocytes and myelin are strongly positive for C1q, C4, and C3, iC3b-neoepitope and C9-neoepitope deposition compared with normal (Singhrao et al. 1999). RT-PCR showed that the classical complement pathway components C1q C chain, C1r, C3, C4, as well as several complement regulators are expressed at considerable higher level in HD brains compared to control. In situ hybridization revealed that microglial cells express higher levels of C3 and C9. Interestingly, the complement anaphylatoxin receptor mRNAs, C5a receptor and C3a receptor, are also strongly expressed in HD caudate. These receptors have been shown to activate microglia and induce their migration (Nolte et al. 1996; Möller et al. 1997). Despite the strong activation of the complement system in HD, it is currently not known what triggers this effect. Potential activators could be apoptotic cells or extracellular aggregated protein released from dying cells.

Neuroinflammation

Neuroinflammation is mediated by soluble pro-inflammatory molecules such as cytokines, prostaglandins, and nitric oxide (NO). Very little is known about these molecules in HD. In a recent report we observed that post-mortem human HD tissue has a distinct profile of inflammatory mediators (Silvestroni et al. 2009). While some inflammatory mediators such as IL-1 β and TNF- α were increased only in the striatum, IL-6, IL-8 and MMP-9 were also upregulated in cortex and, surprisingly, the cerebellum, a CNS region commonly thought to be spared in HD. This is considerably different from the more generalized neuro-inflammatory profile of other neurodegenerative disease such as AD or PD, which show a upregulation of a wide range of inflammatory mediators (Wyss-Coray 2006; Przedborski 2007). We believe that the inflammatory mediators detected in the striatum are a sign of the ongoing pathology, whereas the widely dysregulated factors IL-6, IL-8 and MMP-9 reflect a more generalized effect of htt^{exp}. Indeed we found that IL-6 release is increased in htt^{exp} expressing human HD monocytes, as well as in murine htt^{exp} macrophages and microglia, arguing for a widespread effect of htt^{exp} on immune cells (Bjorkqvist et al. 2008). It is noteworthy to mention that in HD, in contrast to other neurological diseases such as multiple sclerosis and AD, influx of peripheral immune cells such as lymphocytes

or neutrophils has not been reported in neuropathological studies. In fact, we reported that T-cells are not increased in post-mortem human HD tissue (Silvestroni et al. 2009). Therefore, neuroinflammation in HD seems solely sustained by the interactions of microglia, neurons, and macroglia.

The kynurenine pathway

The kynurenine pathway is the primary route of L-tryptophan metabolism in mammals and the central pathway to the formation of nicotinamide adenine dinucleotide (NAD⁺) (Moroni 1999). This pathway contains several metabolites which have neuroactive properties (for review see: Amori et al. 2009; Schwarcz et al. 2010). The kynurenine pathway was first implicated in HD pathogenesis in seminal work showing that intrastriatal injection of quinolinic acid (QUIN) replicates many features of human HD in rodents (Schwarcz et al. 1983). QUIN is an *N*-methyl-D-aspartate (NMDA) receptor agonist and induces neurotoxicity by overstimulation of this glutamate receptor (Schwarcz and Pellicciari 2002). In the subsequent years several studies investigated the levels of kynurenine pathway metabolites in HD and generally found increased levels of neurotoxic metabolites and decreased levels of neuroprotective metabolites in HD patients and HD mouse models (for review see: Giorgini 2008; Schwarcz et al. 2010). Interest in this pathway was rekindled by a surprising finding in a yeast suppressor screen, where genetic deletion of kynurenine 3-monooxygenase (KMO) was found to suppress htt^{exp} toxicity (Giorgini et al. 2005). In the CNS KMO is predominantly expressed in microglial cells and not found in neurons (Guillemin et al. 2003; Giorgini et al. 2008). This finding provided a functional link for microglial involvement in HD pathogenesis and was the first glimpse of a potentially non-cell autonomous mechanism in HD. A follow up study showed that cultured microglial cells from the R6/2 HD mouse model indeed synthesized increased levels of neurotoxic kynurenine pathway metabolites and that these increases can be modulated by histone deacetylase (HDAC) inhibitors (Giorgini et al. 2008). Several academic, nonprofit and commercial projects are now underway to further elucidate the role of kynurenine pathway in HD, as it provides an attractive target for pharmacological intervention (Schwarcz 2004).

Inflammation as a target in HD

While neuroinflammation has been targeted in many neurodegenerative diseases ranging from AD to ALS to PD (Lobsiger and Cleveland 2007; Harry and Kraft 2008;

Rogers 2008; Hirsch and Hunot 2009), it has not received much attention from the HD community. However, several published trials, while not having neuroinflammation per se in mind, might have also targeted this process. For example, experiments using minocycline likely not only targeted caspases and neuronal apoptosis (Chen et al. 2000; Stack et al. 2006), but may have also more broadly targeted neuroinflammation and microglial cells (Harry and Kraft 2008). While the efficacy of minocycline in HD and the mechanisms targeted by this tetracycline derivative is a matter of ongoing debate (Blum et al. 2004; Mievis et al. 2007; Kim and Suh 2009; Orsucci et al. 2009), other drugs with efficacy in HD models such as HDAC inhibitors (Hockly et al. 2003; Thomas et al. 2008) also likely have general anti-inflammatory effects (Dinarello 2006; Kim et al. 2007) or may even target specific microglial processes related to HD (Giorgini 2008). One recent publication, however, seem to have targeted microglial cells more specifically, by using the CNS specificity of microglial cannabinoid receptor 2 (CB₂) expression (Stella 2009). Using CB₂ knockout animals and CB₂ specific agonists, this study showed involvement of CB₂ in reducing neuroinflammation and reversing neuronal loss (Palazuelos et al. 2009). While there is ongoing debate about the expression of CB₂ in microglial cells in vivo (Stella 2009), this study is the first attempt at targeting neuroinflammation in HD.

Microglial [Ca²⁺]_i signaling its potential role in HD

Abnormalities of intracellular calcium ([Ca²⁺]_i) handling is a well documented feature of htt^{exp}-mediated cellular dysregulation (Bezprozvanny 2007). Striatal medium spiny neurons from YAC128 mice show disturbances in stimulation induced [Ca²⁺]_i handling and increased apoptosis (Tang et al. 2005). The [Ca²⁺]_i dysregulation, however, is not limited to neuronal cells. Data from YAC72 and human HD lymphoblasts showed a decreased [Ca²⁺]_i handling capacity of htt^{exp} mitochondria (Panov et al. 2002). Mechanistically, htt^{exp} might exert these effects by interacting with the Inositol-3-phosphate receptor 1 (InsP₃R1), binding to the outer mitochondrial membrane, interaction with voltage gated Ca²⁺ channels (VGCCs) or the NMDA receptor (Bezprozvanny 2009). Microglia [Ca²⁺]_i signaling has mainly been studied in response to external stimuli (Möller 2002; Farber and Kettenmann 2006). However, recent data suggests that similar to other immune cells, persistent increases in microglial [Ca²⁺]_i from ~80 to ~150 nM occur during activation and influence central microglial effector functions such as cytokine release (Hoffmann et al. 2003). While data on the effect of increased microglial [Ca²⁺]_i on downstream functions remains scant, the large body of data on other immune cells such as T lymphocytes

suggest that small, long-term changes in basal [Ca²⁺]_i (Δ40 nM) trigger the activation of transcriptional programs, which ultimately lead to changes in the cell phenotype (Im and Rao 2004; Quintana et al. 2005). Htt^{exp}-mediated changes in microglial basal [Ca²⁺]_i, similar to what has been reported in neurons, could therefore lead to longterm changes of microglial transcriptional programs, including some that might detrimentally affect neighboring neurons.

Outlook

It is becoming increasingly clear that neuroinflammation is an integral component of HD. Htt^{exp} is expressed in microglial cells, the central effectors of neuroinflammation, and this expression alters several of the baseline parameters of these cells. However, the mechanism/s by which htt^{exp} causes the reported changes in microglial physiology is not well understood and thus is at the center of ongoing investigations in our and several other laboratories. Techniques similar to what has been employed to investigate neuronal transcriptional abnormalities (Cha 2007) will further our understanding on how htt^{exp} effects the microglial transcriptome. More microglia-specific queries should shed light on changes to cytokine release, migration or phagocytosis in HD. Disruption of normal microglial functions, together with microglial activating tissue signals indicative of neuronal distress, might lead to an ill-adapted neuroinflammatory response. This inflammatory response may contribute to the death of additional neurons and subsequently more neuroinflammation, in a self-sustaining process. Independent of the underlying mechanism (cell autonomous, cell-cell interaction or both), neuroinflammation “will make a bad thing even worse”. Once better understood, targeted interference with neuroinflammatory processes, active or reactive, could be a valuable tool for developing new therapeutic approaches.

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