Review

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The choreography of neuroinflammation in Huntington's disease

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Currently, the concept of 'neuroinflammation' includes inflammation associated with neurodegenerative diseases, in which there is little or no infiltration of blood-derived immune cells into the brain. The roles of brain-resident and peripheral immune cells in these inflammatory settings are poorly understood, and it is unclear whether neuroinflammation results from immune reaction to neuronal dysfunction/degeneration, and/or represents cell-autonomous phenotypes of dysfunctional immune cells. Here, we review recent studies examining these questions in the context of Huntington's disease (HD), where mutant Huntingtin (HTT) is expressed in both neurons and glia. Insights into the cellular and molecular mechanisms underlying neuroinflammation in HD may provide a better understanding of inflammation in more complex neurodegenerative disorders, and of the contribution of the neuroinflammatory component to neurodegenerative disease pathogenesis.

A comprehensive concept of neuroinflammation

The concept of 'neuroinflammation' was used originally to describe inflammatory settings of the central nervous system (CNS) characterized by infiltration of peripheral immune cells, such as viral and bacterial infection, ischemic stroke, HIV encephalopathy, and multiple sclerosis (MS) [1,2]. Currently, the same term has expanded to include neurodegenerative diseases that do not attract inflammatory cells from the blood. Alzheimer's disease (AD), Parkinson's disease (PD), and HD are characterized by cellular and molecular features of inflammation (cytokine expression and microglia activation), but lack the signs of classic 'neuroinflammation', such as immune cell infiltration from the blood stream [1–5]. Nevertheless, the absence of immune cell infiltration from the periphery does not rule out the potential contribution of these cells to neuroinflammation, for example, via a chronic increase of systemic proinflammatory cytokine production. Furthermore, whether inflammation is the response of surrounding cells to a neuron-autonomous degenerative process and/or due to cell-autonomous immune activation remains an area of active investigation.

Glial cells are non-neuronal cells in the brain that play diverse roles in tissue homeostasis and support of neuronal function. For the purposes of this review, we focus on two types of glial cell: microglia and astrocytes (see Glossary). Under conditions of infection or injury, these cells become 'activated', a process characterized by their production of numerous mediators that promote inflammation, changes in morphology, and, in some cases, cell division, resulting in increased cell numbers or 'gliosis'. Regardless of the mechanisms responsible for glia activation, the contribution of inflammation to neurodegenerative diseases pathogenesis remains poorly understood. In contrast to PD and AD, which are complex multifactorial pathologies related to a spectrum of genetic mutations and environmental factors [3,4], HD or Huntington's chorea, is a neurodegenerative disorder caused by a single mutation: a specific expansion of the PolyQ tract in the ubiquitously expressed HTT protein [6]. Interestingly, even though HTT protein is constitutively and ubiquitously expressed throughout the body, *HTT* mRNA expression in immune cells is on average higher than that observed in most organs (Genomics Institute of Novartis Research Foundation, transcript 202389_s_at)

Glossary

Astrocyte: the most abundant type of glial cell in the brain. Astrocytes play numerous roles in supporting neuronal function and establishing the blood–brain barrier.
Chemokine: a group of small proteins within the broad category of cytokines that are released from cells and result in directed migration of nearby cells. Cytokines play important roles in attracting immune cells to sites of injury and infection.
Cytokine: a broad category of small proteins that are released from cells and exert biological effects on target cells. A subset of cytokines, including molecules such as TNFα and IL-6, are released from activated microglia and astrocytes and promote inflammatory responses.
Damage associated molecular pattern (DAMP): this term refers to endogenously derived molecules that are recognized by pattern recognition receptors as indicators of tissue injury.
Gliosis: a histological term referring to an increase in the number of glial cells in the brain accompanied by morphological changes associated with glial activation.
Microglia: the major resident macrophage population in the brain. In addition to contributing to tissue homeostasis, microglia play primary roles in sensing injury and infection through expression of pattern recognition receptors.
Monocyte: a circulating innate immune cell that can migrate into tissues in response to infection or injury and differentiate into a macrophage.

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[7]. In recent years, several efforts have been made to understand whether mutant HTT expression could trigger cell-autonomous activation of the immune cells of the brain and periphery, and whether these, in turn, could negatively impact HD pathogenesis. Here, we review recent evidence on the impact of mutant HTT on microglia, astrocytes, and macrophages. We place these findings in the context of the current understanding of inflammation in HD, and discuss the potential contributions of these cells to HD pathogenesis.

Clinical features of neuroinflammation in HD

Accumulation of reactive microglia and astrocytes has been observed in brains from HD patients [8]. PET imaging showed that microglia activation correlates with the pathology in HD patients [9–11]. Activation of microglia is evident in presymptomatic HD gene carriers, and can be detected up to 15 years before predicted age of onset [10], approximately the same time frame when increased levels of interleukin (IL)-6 are observed in the plasma [12]. Microglia activation in tissue specimens is typically characterized by increased numbers of microglia and morphological changes, in which the extensive cytoplasmic ramifications characteristic of resting microglia are retracted, resulting in an ameboid appearance. These morphological changes are associated with increased production of cytokines, such as IL-6. Intriguingly, the plasma level of IL-6 is correlated with disease severity based on a scale of functional capacity [12]. In patients' striatum and cortex, reactive microglia accumulate in relation to the degree of neuronal loss [10]. Reactive microglia are clearly seen even in low-grade HD human brains, suggesting an early microglia response to changes in axons [10]. Interestingly, it has been reported that activated microglia proliferate at neurites of mutant HTT-expressing neurons *in vitro*. Significant microglia activation in regions related to cognitive function in HD patients has recently been suggested to predict disease onset [13].

The cerebrospinal fluid of HD patients exhibits evidence of immune activation, with upregulation of IL-6, IL-8 and tumor necrosis factor (TNF)-α [12]. Significant signs of oxidative stress have been reported in postmortem brain specimens from HD individuals. Early studies reported a decrease in several mitochondrial enzymes involved in respiration [14], as well as loss of aconitase activity in caudate and putamen in symptomatic patients with striatum atrophy [15]. Protein carbonyls, markers of oxidative stress, appear to be increased in HD brains, indicating that reactive oxygen species (ROS) are overproduced [16]. In addition, increased levels of 3-nitrotyrosine, a sign of reactive nitrogen species (RNS), have been observed in HD cortex and striatum [17]. By contrast, antioxidant defense proteins, such as peroxiredoxins 1, 2, and 6, as well as glutathione peroxidases 1 and 6, are strongly induced [16]. Furthermore, iron, a metal involved in mitochondria metabolism as well as in ROS generation, appears to accumulate in the brains of HD patients [18].

Patients with HD also show multiple systemic changes [19], including alterations in the function of the peripheral immune system. Increases in expression of genes that are produced by innate immune cells have been observed, such as the gene encoding immediate early response 3 mRNA (*IER3*) [20]. In addition, blood levels of several proteins produced by innate immune cells correlate with disease progression [21]. In particular, a significant elevation of chemokines Chemokine (C-C motif) ligand (CCL)-2, CCL4, CCL11, CCL13, CCL26, matrix metalloprotease (MMP)-9, vascular endothelial growth factor (VEGF), and transforming growth factor (TGF)-1β have been detected in the plasma from HD patients [22,23]. By contrast, plasma levels of IL-18 were significantly reduced in HD patients in comparison with controls [22]. Also the level of thioredoxin reductase-1 and thioredoxin-1 appeared to be decreased in plasma and erythrocytes from HD individuals [24]. Of note, it has been reported that the active form of signal transducer and activator of transcription (STAT)-5, a transcription factor commonly used by several cytokines, is increased in monocytes from HD patients at baseline [25]. Collectively, these observations suggest that expression of mutant HTT in peripheral immune cells results in cell-autonomous effects on their gene expression patterns and function. Whether these alterations contribute to disease severity is unknown at present, but serum levels of cytokines could potentially serve as biomarkers to assess efficacy of anti-inflammatory interventions.

The most interesting biomarker for HD-associated inflammation may be mutant HTT itself. In monocytes and T cells, mutant HTT levels were significantly associated with disease burden score and caudate atrophy rates in HD patients [26]. However, no infiltration of circulating innate or adaptive immune cells has been reported in postmortem HD brain samples [5]. At present, only two studies have reported the presence of autoantibodies in HD. In the first report, autoantibodies directed against gliadin, a protein component of gluten, were observed in 44.2% of HD patients [27]. The second report showed alteration in the titers of an antibody to angiotensin II type 1 receptors (AT1R); this antibody promoting dysfunction of the adaptive immune system [28]. MS patients show increased titers of anti-AT1R in comparison with matching controls. HD individuals showed the presence of anti-AT1R more frequently than in controls and in MS patients as well. In 37.9% of HD patients, titers were >20 U/ml. The presence of autoantibodies suggests the possibility of a failure in immune tolerance in HD. Further studies are needed to determine whether dysfunction in the adaptive immune compartment is present in HD.

The role of microglia in HD neuroinflammation

Microglia, accounting for less than 10% of the total brain cells [29], represent the major population of resident immune cells of the CNS [30]. In healthy brains, microglia are characterized by a small cell body and ramified processes. Such 'patrolling-mode' [31] microglia contribute to brain homeostasis through phagocytosis, scavenging activity, secretion of homeostatic factors, such as TGFβ, and synaptic pruning [30,32]. In response to infection or tissue damage, microglia rapidly alter their morphology to an 'ameboid' appearance, increase phagocytic activity, and initiate an innate immune response by secreting various inflammatory molecules, including IL-6, and TNFα [30,32]. Once the inciting stimuli have been eradicated,