Current understanding of the glial response to disorders of the aging CNS

Roger A Barker1* and Francesca Cicchetti2,3 *

1 Department of Clinical Neuroscience, Cambridge Centre for Brain Repair, University of Cambridge, Cambridge, UK
2 Centre de Recherche du CHUL (CHUQ), Axe Neurosciences, Québec, QC, Canada
3 Département de Psychiatrie et Neurosciences, Université Laval, Québec, QC, Canada

Edited by: Ian M. Stanford, Aston University, UK
Reviewed by: Jason B. Wu, Cedars-Sinai Medical Center, USA
Raja S. Settiavari, The Dow Chemical Company, USA
Correspondence: Roger A Barker, Cambridge Centre for Brain Repair, University of Cambridge, Cambridge, CB2 0PY, UK; e-mail: rab46@cam.ac.uk; Francesca Cicchetti, Centre de recherche du CHUQ (pavillon CHUL), 2705 Boulevard Laurier, T2-50, Québec, QC, Canada; e-mail: francesca.cicchetti@crchul.ulaval.ca

In this special issue of Frontiers in Pharmacology, we have asked leading experts to comment and review the evidence that inflammatory cells play a leading role in the pathological processes underlying neurodegenerative disorders. We now seek to draw these various observations together into a conclusion, with the hope that this will inform further work in this area and result in the identification of new therapeutic targets that will have a disease modifying effect.

Keywords: inflammation, microglia, Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, motorneuron disease

INTRODUCTION

For many years, chronic neurodegenerative disorders of the central nervous system (CNS) were thought of in terms of primary neuronal dysfunction and loss with secondary glial and inflammatory responses. These responses were defined by an astrogliosis and the presence of a few activated microglia, but of late this theory has required revision.

Microglia, which account for approximately 10% of the adult brain cell population, were first described by Pio Del Rio Hortega in 1919 (McGeer and McGeer, 2012) and their identity as a discrete cell population was met with great skepticism. Nevertheless, the recognition of microglia as a distinct cell type was taken on by Ralph van Furth who proposed that they may have some function akin to phagocytes found in other parts of the body. However, it was not until the late 1980s that this field came of age when, using the new technique of immunohistochemistry, the McGeers showed that within the Alzheimer’s disease (AD) brain there were large numbers of activated HLA-DR II positive microglia (McGeer et al., 1987). This paper, which struggled to find its way into publication, has now been cited many hundreds of times and paved the way for a whole new area of work on the glial response in neurodegenerative disorders. This first demonstration of class II positive microglial cells in AD led to further discoveries of such cells in a whole range of different neurodegenerative disorders and with it the concept of neuroinflammation. The pioneering work of the McGeers was to radically change how these diseases were seen as they went on to show that microglia were not only intimately bound to central inflammatory responses and antigen presentation, but in fact the whole innate immune system itself had a role to play in these CNS disorders.

We now know that microglia continuously and actively survey the CNS microenvironment (Nimmerjahn et al., 2005), although their distribution is not uniform across the brain which may impact on their pathogenic capacity in different disease states (Lawson et al., 1990). They arise from the primitive myeloid progenitors and enter the developing CNS during embryogenesis and continue to be produced throughout life, sharing many similarities to peripheral macrophages. The original description of the phagocytic properties of microglia was taken to show that their primary function was to remove dying and dead cells and by so doing prevent the release of pro-inflammatory cytokines, chemoattractants, and infiltrating T-cells. However, it is shown that under certain conditions, activated microglia can actually phagocytose viable neurons and synapses and that this may be especially prominent in areas of CNS neuroinflammation as is seen in many, if not all, neurodegenerative disorders (Neher et al., 2012). This would fit well with their role in synaptic pruning in normal development as well as their emerging role in plasticity in the normal brain (Tremblay et al., 2011). In addition, microglia have an important role in adult neurogenesis through their ability to remove apoptotic cells and by so doing allow the integration of those cells that survive and mature into neurons [reviewed in Ekdahl (2012)]. Thus microglia have a repertoire of roles throughout life in the CNS.

MICROGLIA AND ALZHEIMER’S DISEASE

An appreciable number of brain diseases seem to share the common feature of a marked glial response and in this respect the role of microglia in AD has been particularly well studied following on from the original observations of the McGeers (McGeer et al.,...
This disorder, the most common of the chronic neurodegenerative diseases, typically presents with an evolving amnestic syndrome and is characterized pathologically by the deposition of extracellular beta-amyloid plaques and intracellularly by tau tangles. The way in which these two pathologies interact with each other to cause disease is unclear, as is how they relate to the inflammation seen within the brains of patients dying with AD. Nevertheless, it is known that inflammation starts early in the disease process, probably ahead of any obvious amyloid deposition [reviewed in Politis et al. (2012)] and at post-mortem there is a substantial inflammatory response especially around the Aβ plaques. Indeed, Aβ itself can activate microglia which in turn can phagocytose neurons, suggesting that microglia are a critical determinant of neuronal cell loss in this condition (Fuhrmann et al., 2010). Neuroinflammation has also been linked to tau-mediated neurodegeneration as well.

For many years, though, the role of inflammation in AD, whilst being recognized as being present, was always relegated to be a secondary or downstream event. However, the recent GWAS in AD have shown that a number of genetic loci linked to the disease possibly code for inflammatory factors (Harold et al., 2009), which implies that they may be much more intimately involved in the actual disease process. In this respect, it is of interest to note that systemic inflammation can also influence what happens within the CNS, which has led some investigators to propose that it may be a critical initiating factor in the genesis of disorders such as AD, and it is through this non-CNS route that the GWAS loci mediate their susceptibility effects (Ransohoff and Perry, 2009).

Whilst microglia responses can be thought to be detrimental to neuronal viability and survival, it is possible that some of the microglia responses may actually be neuroprotective by virtue of the fact that they could help clear Aβ, remove damaged cells and secrete a range of growth factors and anti-inflammatory agents [reviewed in Solito and Sastre (2012)]. Whilst all this may be the case in the young CNS, there is now an emerging concept that AD results primarily from microglial senescence and a progressive breakdown of innate CNS immunity. This is because the major function of microglia is a neuroprotective one given their ability to phagocytose pathogens, secrete neurotrophic factors as well as dampen down free radical production and sequester glutamate in conjunction with astrocytes. Indeed, the astrocytic response has an equally important role in AD pathogenesis with evidence that astrocytes and neurons can interact in a vicious cycle of chronic, sustained, progressive neuroinflammation and cell death. For example, in advanced stages of AD, it has been shown that TRAIL secreted from astrocytes binds to death receptors on neurons to trigger apoptosis (Li et al., 2011). All of this complexity of action of inflammatory cells in an aging CNS presents a challenge in knowing how best to target them therapeutically in AD.

MICROGLIA AND PARKINSON’S DISEASE
Parkinson’s disease (PD) has long been described clinically through its motor manifestations of a resting tremor, rigidity, and bradykinesia and, pathologically, by the formation of alpha synuclein positive Lewy bodies in the substantia nigra with the loss of the nigrostriatal dopaminergic projection. However, it is now clear that the pathology, and the clinical features of PD, are much more extensive and that the disease may even start outside the CNS (Ferrer et al., 2011). This change in our understanding of the extent and pattern of evolution of PD pathology has led to a re-examination of the pathogenic process and with this the potential role for inflammation and microglia, as first suggested by McGeer et al. (1988a) as early as 1988.

Several studies have now shown that microglial activation and elevated levels of inflammatory cytokines accompany neurodegeneration in PD patients (McGeer et al., 1988b; Mogi et al., 1994, 1995a; Banati et al., 1998). For example, Langston et al. (1999) in the post-mortem analysis of MPTP intoxicated patients and Brownell et al. (1999) in primates exposed to the same toxin, pointed to the possibility of an inflammatory and glial response in MPTP induced nigral cell death [also see review by McGeer et al. (2001)]. Subsequent studies have confirmed that activated microglia can be seen in the brains of patients with idiopathic PD both using PET imaging [reviewed in Politis et al. (2012)] and pathologically (reviewed in Huang and Halliday (2012)). These changes occur early in the disease course and thereafter remain stable, which suggests that they may be an important initiating event (Ouchi et al., 2005). In this respect, it has now been shown that in animal models of PD, dopaminergic cell loss can be induced solely by inflammatory insults (e.g., Lipopolysaccharide, LPS; Cicchetti et al., 2009a) and that in more traditional neurotoxin induced animal models of PD, inflammation may be necessary for the full expression of the lesion (e.g., Drouin-Ouellet et al., 2011). Furthermore, it has been shown that α-synuclein itself can directly activate microglia (Zhang et al., 2005), and that many of the gene products from the mendelian forms of PD, not only have a role in the intracellular handling of PD related proteins, but also in modulating innate immune signaling (Huang and Halliday, 2012). This sits well with the recent genetic studies linking PD to HLA (Hamza et al., 2010; Saiki et al., 2010). Finally it is worth noting that activated microglial cells in PD are predominantly found in proximity to a key sign of aging namely free neuromelanin (McGeer et al., 1988b) – again highlighting the complex interplay between microglia, disease processes, and an aging CNS.

Other inflammatory cells, such as astrocytes, may also be important in PD not only by virtue of their known ability to support normal neuronal function but also through a role in maintaining the integrity of the blood brain barrier (BBB; Halliday and Stevens, 2011). This may be especially important as abnormalities in this structure (namely the BBB) could allow other parts of the immune system to gain access to the CNS and by so doing contribute to the pathology seen in PD (Kortekaas et al., 2005).

MICROGLIA AND HUNTINGTON’S DISEASE
Huntington’s disease (HD) is a rare autosomal dominant disorder characterized by motor, cognitive, and psychiatric problems with extensive pathology across the CNS. Driven by this dominant genetic mutation in the huntingtin gene, the neuropathological signs of HD are visible in many structures of the CNS, but predominantly within the striatum and cortex from an early stage of disease. This prominent neuronal loss is accompanied by protein aggregates composed of the mutated form of the huntingtin protein and with this there is significant activation of microglia (Sapp
et al., 2001). This activation has been shown in both premanifest (Tai et al., 2007) and manifest HD patients (Sapp et al., 2001) and there appears to be a correlation between the level of microglial activation and disease severity (Pavese et al., 2006), all of which suggests that the microglia are intimately involved in the disease process in HD.

There is now emerging evidence that the ubiquitous expression of the mutant huntingtin protein affects the function of cells outside the CNS. In particular, the mutant huntingtin protein interacts with the immune system with accumulating evidence that changes in this system may critically contribute to the pathology of HD. However, the nature of this contribution remains unclear, to the extent that it is not even known whether the immune system plays a beneficial or detrimental role in HD patients (Soulet and Cicchetti, 2011). What is clear is that analysis of blood samples from HD patients shows abnormal release of pro-inflammatory cytokines in early stages of the disease (Bjorkqvist et al., 2008).

The astrocytic response in HD is substantial and in fact defined early descriptions of the pathology. Indeed the original grading system of striatal atrophy and disease severity by Vonsattel et al. (1985) used this response. This work also highlighted how the astrocytic response follows neuronal loss such that the striking striatal atrophy following a dorso-ventral pattern is mirrored by the intensity of the astrocytosis.

As in the other neurodegenerative conditions we have discussed, the glia are not passive bystanders to the disease process, but seem to be an integral part of the pathological process from the time of disease onset.

**MICROGLIA AND MOTORNEURON DISEASE**

Motorneuron disease covers a range of disorders all of which are characterized by the loss of motorneurons (MNs), and the extent to which this selectively targets the upper or lower MN defines the disease type, e.g., primary lateral sclerosis (PLS) for a pure upper motor neuron (UMN) disorder while spinal muscular atrophy (SMA) singles out the lower motorneurons (LMNs). However, the commonest type involves both UMN and LMNs and is termed amyotrophic lateral sclerosis (ALS), and whilst there are known genetic forms of this disorder, the vast majority are sporadic in nature (Talbot, 2011). Nevertheless, the rare genetic forms of ALS, especially those with mutations in SOD1, have been used to model the disease in the laboratory and of late this has led to studies where the mutant gene has been differentially expressed in various cellular compartments within the CNS. These studies have clearly shown that the effects of the mutant gene in non-neuronal cells is not insignificant, and coupled to the pathological findings in patients dying with ALS, has suggested that the disorder is one that is critically dependent on events in neurons, astrocytes, and microglia (Phani et al, submitted).

Within the MN itself, many pathogenic pathways, which compromise that cell – subsequently leading to dysfunction and death – have been postulated (Ince et al., 2011). These pathways involve the production of abnormal reactive oxidative species (ROS) which in turn compromises mitochondrial function, energy production, and cell integrity. This abnormal production of ROS is enhanced in SOD mutant cells and can further be exacerbated by excessive glutamate stimulation of the MNs and calcium influx. These latter processes may be in part mediated by abnormal glutamate handling by astrocytes, as further supported by studies demonstrating the beneficial effects of glial cell grafts in transgenic models of ALS (Lepore et al., 2008).

In addition, whilst the astrocyte-neuron interactions may be a critical component in the disease process, it is also known that in the brains of patients dying with ALS there is a marked microglial response. As is common to other neurodegenerative disorders, the question arises as to where this reaction lies in the causal cascade of pathogenic events and whether this changes over time. In this respect, there is evidence in animal models that minocycline can have deleterious effects on microglia and astrocytes once the disease has begun (Keller et al., 2011), which is in line with a clinical study of this drug in ALS showing that it was ineffective and even harmful (Gordon et al., 2007). As such, it is likely that the microglia, as with the astrocytes, do play a role in the loss of MNs in ALS, although the extent to which selectively targeting them therapeutically will truly change the disease course is less clear. What is clear however, is that in ALS, the disease is not localized to the motorneuronal compartment and as such, strategies designed around studying patient specific induced pluripotent stem cell derived MNs may only give partial answers. This is especially true if such assays are being used for patient selective drug screens (Ebert et al., 2009).

**INFLAMMATORY CELL TARGETING FOR FUTURE THERAPEUTIC APPROACHES TO NEURODEGENERATIVE DISORDERS**

Initial views on the role of microglia suggested that these cells were simply there to scavenge up debris and dead cells, while astrocytes fulfilled some supportive role in the CNS. However, microglia are now recognized to have a complex array of supportive and destructive roles in the CNS and that the balance between the two may be critical in driving some aspects of disease processes. Astrocytes are now seen as being fundamental in shaping and maintaining the developing and mature CNS, including a role in adult neurogenesis, axonal regeneration, and the BBB. The dynamic interplay between all of these different CNS compartments is becoming more evident, such that some neurodegenerative disorders of the CNS may have a pathology as much in the glial cells as in the neurons themselves. This all means that understanding what happens in disease states is far more complex than originally conceived and that targeting each element of the interaction may be the route by which true disease modification can be achieved.

In this special issue of Frontiers in Pharmacology we have repeatedly seen how the glia, immune response, and neurons interact to drive disease, and that our abilities to more accurately define and follow this in vivo has enabled us to better understand the temporal relationships that exist between these cellular players and when and how they can best be modulated for therapeutic benefit. Indeed, our capacity to better visualize the glial cells in patients with neurodegenerative disorders especially with respect to microglia is well covered by Politis et al. (2012). This is particularly important given the limitations of animal models of neurodegeneration which includes the fact that they often model disease using a transgenic approach, even though the commonest neurodegenerative disorders (AD and PD) are largely sporadic in...
nature. In addition, these animals typically develop disease over weeks and months when in patients they evolve over months or years, and thus short acute therapies in the laboratory may not be relevant to the clinic. Finally, our capacity to better define the heterogeneity of patient populations has meant that the therapeutic idea that “one size fits all” is no longer tenable, and that disease processes may follow very different trajectories in different patients and as such require completely different therapeutic approaches (see, e.g., Williams-Gray et al., 2009). A point reinforced by the heterogeneity of glial responses as a function of age and disease state.

As we move toward an era of ever more sophisticated therapeutic agents, our ability to better understand networks of disease pathogenesis will become increasingly important as our capacity to dissect the role of each component will be critical to the success of any such therapy. This is perhaps best shown in the world of cellular transplants for HD, where simply delivering a cell replacement therapy to a diseased brain may not be useful in itself, not because there is anything intrinsically wrong with replacing dysmorphic pathways, but because the necessary support for those cells is no longer there and may even be replaced by a hostile environment (Cicchetti et al., 2009b, 2011). It has even been proposed and demonstrated that in some animal models of motorneuron disease, transplanting glial cells is better than trying to replace the MNS per se, as the former have a more critical role in disease pathogenesis through their handling of glutamate (Lepore et al., 2008).

In conclusion, there is now a growing body of evidence from many different sources demonstrating that glial and inflammatory responses are central to these diseases – this includes findings from epidemiological studies looking at anti-inflammatory drugs and the risk of PD and AD; the GWAS in AD and PD; pathological and imaging studies in patients as well as the study of peripheral markers of inflammation [e.g., in HD – reviewed in Wild et al. (2008)]. All of this makes for a very persuasive role for the glia and inflammation in chronic neurodegenerative disorders of the CNS, which will set the scene for a whole new approach to disease modifying therapeutics for a group of disorders that will become increasingly more common as the population ages. Exactly what form these agents will take is unresolved but may involve using drugs that are already in clinical use such as minocycline and non-steroidal anti-inflammatory drugs (NSAIs). Indeed, the use of anti-inflammatory agents for treating AD has long been considered, outside of the amyloid immunization approach (Menendez-Gonzalez et al., 2011). Their efficacy has yet to be proven especially with respect to the commonly available NSAIs which appear to be much less effective in controlling the activation of aged, as compared to young microglia and are likely to be too wide-spectrum thereby suppressing both the detrimental (e.g., pro-inflammatory cytokines, oxidative stress, etc.) and beneficial roles (e.g., pro-repair processes, phagocytosis, and neuroprotection) of the immune cells (Soulet and Cicchetti, 2011). Thus selecting the right agent in the right aged patient group at the right stage of their disease will be critical, and as our understanding of the role of microglia, astrocytes and other related cells evolves, and how they relate to each other; so will our capacity to target them in disease settings.

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