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Special issue commentary: The changing face of inflammation in the brain☆

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ABSTRACT

The study of inflammation in the brain has been extended to include a wide range of conditions, but there remains plenty of argument over semantics and the precise definition of what constitutes inflammation in these pathologies. In this special issue, we sought to highlight the diversity of what is considered to be inflammation in the brain, and we have accepted that the presence of microglia cells with altered morphology remains a useful starting point. However, it is clear that whatever is the molecular expression profile that accompanies an activated microglial cell, it is not static and it is influenced by factors both intrinsic and extrinsic to the brain. This article is part of a Special Issue entitled 'Neuroinflammation in neurodegeneration and neurodysfunction'.

"The difficulty lies, not in the new ideas, but in escaping the old ones."John Maynard Keynes

In the context of demyelinating disease, the study of neuroinflammation dates back to the 1930s (Rivers and Schwentker, 1935). However, it was the recognition, now 20 years ago, that microglial activation alone can often be the defining histopathological feature of the presence of inflammation in the brain that has changed the way in which we view the contribution of the immune system to a spectrum of neurological disease (Andersson et al., 1991). The early experiments demonstrating that the CNS inflammatory response to acute neuronal cell death is atypical when compared with the response to cell death elsewhere in the body involved the generation of focal excitotoxic lesions in the brain. In these experiments, very little leukocyte recruitment was observed and the only overt myeloid cell response to be seen was the activation and proliferation of microglial cells. Over time this led to a wide acceptance that the CNS inflammatory response, where present, might be solely characterised by the presence of microglial activation and that this activation was likely to contribute, in a detrimental fashion, to the outcome of brain pathology (Blasko et al., 2004). This view was consistent with Metchnikov's biological theory of inflammation, which centred round the phagocyte as the primary effector cell (Letiembre et al., 2009). In multiple sclerosis (MS), widespread 'extralesional' axonal injury in grey matter has been shown to co-localise with activated microglia and supports this view of activated microglia as potentiators of CNS disease (Howell et al., 2010; Politis et al., 2012). It should be noted that the first experiments describing the atypical nature of the CNS inflammatory response came at a time when the origin of microglia was still a matter of debate (Fedoroff et al., 1997). Indeed, the origin of the microglial population has remained a contentious issue: not that they are or are not of myeloid origin (Gomez Perdiguero et al., 2012), but whether they are maintained as an ontogenically distinct population in the mononuclear phagocyte system (Ginhoux et al., 2010). It remains to be determined whether this might have any functional impact on the behaviour of microglia compared to recruited monocytes that quickly adopt a microglial phenotype. However, as discussed in the reviews contained in this special issue it is clear that our view of what neuroinflammation is, or is not is being continuously revised and refined.

Microglial activation is a necessary, but not sufficient feature, to define neuroinflammation. It is now clear that microglia can look active, amoeboid rather than stellate, in the absence of pro-inflammatory cytokine production (Perry et al., 2007). Thus, inference of the activation state of microglia, or astrocytes for that matter, from morphology alone has proved unsafe. In vitro studies have recognised that macrophages may be polarised into distinct subpopulations on activation depending on the nature of the stimulus (Martinez et al., 2006). Macrophages are now often classified as either resting, or they may be stimulated to exhibit an M1-type classically-activated (pro-inflammatory) phenotype following LPS and IFN-γ treatment, or to an M2-type alternatively activated (phagocytic) phenotype following treatment with IL-4 (Martinez et al., 2006). As a resident macrophage population, microglia can also be polarised to produce distinct cytokines profiles (Mikita et al., 2011). M1 microglia make pro-inflammatory cytokines, such as IL-1β and TNF, and COX-2 following classical activation and are viewed as having significant destructive potential in the brain, and M2 microglia have been shown to synthesise COX-1 and TGFβ, and are considered reparative (Olah et al., 2011). This has led to plenty of discussion on how microglial populations might be polarised in distinct CNS pathologies where morphological activation has long been observed (Kigerl et al., 2009). However, much in the same way that the Th1, Th2 and Th17 classifications of immunological lesions are a gross oversimplification of the capacity of distinct T-cell populations to fine tune an immunological response (Rook, 2001), the M1/M2 classification seems even more likely to lead to misconceptions about the behaviour of macrophages and microglia. Indeed, sub-populations of M2-type activation have been described (Graff et al., 2012). The in vitro concept of M1 and M2 activation does not translate particularly well to real-life inflammatory lesions in vivo where the local environment experienced by individual resident cells will change over relatively short distances.

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Indeed, a comparison of macrophage expression profiles in atherosclerosis, MS, and in Gaucher disease reveals that environment rather than 'activation' mode regulates macrophage characteristics (van Eijk et al., 2010). Any lesion is likely to consist of a mixed population of M1 or M2 macrophages and, in all likelihood, many other subtypes as well. The expression of cytokines produced in any given lesion will be mixed, and while it may be true that one profile may dominate, the overall affect will lie somewhere in between the M1 and M2 phenotypes. Even this view will be misinterpreted as suggesting that the macrophage molecular expression profile will rest on some linear molecular continuum between the M1 and M2 phenotypes. There is little evidence for this, and plenty of evidence to suggest that the macrophage factory machine will produce a distinct molecular profile as a response to the changes in the environment in which it finds itself (van Eijk et al., 2010). The polarisation concept also fails to take a number of other important variables such as, the level of activation within any given subtype, the age and origin of the macrophage, the populations and proportions of other leukocyte populations present, and the potential for a macrophage or microglial cell to move between different activation states. However, the concept of 'priming' has attracted recent attention (Cunningham et al., 2005) and suggests that microglia are perfectly able to move between subtypes. In murine prion disease, microglia retract their processes and become very conspicuous in immunohistochemical stains for iba-1 or other commonly used microglial markers (Betmouni et al., 1996; Broom et al., 2007). However, in this state, these morphologically activated cells do not make IL-1β at the protein level unless they are exposed to a further challenge such as the peripheral administration LPS (Walsh et al., 2000, 2001). In this case, the microglia begin making interleukin-1β protein, which may contribute to increased neurodegeneration. This has been shown to be true in other pathologies where microglia look activated, but do not make appreciable amounts of proinflammatory cytokines (Couch et al., 2011; Depino, 2006; Palin et al., 2008). Importantly, at this stage we do not know how long this switch lasts, whether it is a step function or a graded response, whether it may have neuroprotective component, or whether it can be repeated multiple times.

In conclusion, the functional consequences of microglial activation cannot be ascribed to a particular morphology and even microglial cells with differing functional properties may co-exist with each other during neurodegenerative processes. Despite this interpretation, which may seem too complex to predict the functional contribution of neuroinflammation in a given disease, a wealth of data based on solid, unbiased observations have been generated in recent years defining a prominent role for neuroinflammation in a spectrum of CNS pathologies. Microglial behaviour clearly differs in the parenchyma, ventricular, and perivascular areas. The tenets governing the contribution of neuroinflammation to brain pathology also depend on whether there is n accompanying infiltration of peripheral immune cells in the brain, which may be significantly affected by non-CNS comorbidities. In turn, the presence of neuroinflammatory disease is likely to affect the peripheral immune responses in other organs, creating a mutually affected functional circle of physiological relevance.

The interaction between microglia in the brain and systemic immune events is the primary focus of this special issue, which considers, not only how peripheral infection or disease impacts on the pathogenesis of pre-existing brain pathology, but also how the presence of CNS disease can alter peripheral immune events.

The issue begins with an examination of the contribution of systemic inflammation to the pathogenesis of MS by Ferrari, which was, perhaps, one of the first CNS pathologies in which systemic infections were found to be associated with aggravation of disease (Sibley et al., 1985). Our view of MS pathogenesis has altered dramatically in recent years. It has been known for decades that axonal degeneration occurs in MS, but it is only in recent years that evidence has emerged demonstrating that axonal injury and degeneration occur early in the disease and there is evidence from magnetic resonance spectroscopy (MRS) and histological studies that widespread axonal injury occurs within grey and normal appearing white matter, where activated microglia appear to be causing the damage (Howell et al., 2010). Thus, factors that alter the behaviour of microglial at the extralesional sites are of the utmost importance. In the review, the authors highlight the increase in serum levels of cytokines that occur during the relapse phase (Edwards et al., 2011; Mikulkova et al., 2011; Trenova et al., 2011) and how peripheral leukocyte populations are markedly altered during a relapse, which is likely to have profound affects, not only on the CNS pathology, but also on the any other comorbidities. This increase in peripheral cytokine expression may also contribute to the altered perception of pain and wellbeing experienced by individuals with MS now that we understand that peripheral cytokine expression can be as important, if not more so, than CNS cytokine expression in modifying behaviour associated with focal inflammatory lesion in the brain. For example, it has been shown that the inhibition of peripheral TNF expression suppresses sickness behaviours induced by central cytokine administration (Jiang et al., 2008). It is also worth noting that not all of the pathology in MS is restricted to the CNS; we have shown that the number of leukocytes significantly increases in the liver in individuals with MS, which highlights the multi-organ nature of MS pathophysiology and the potential to influence progression by targeting peripheral events (Campbell et al., 2010).

In this issue, two reviews are presented on stroke, which should be read back-to-back to appreciate the implications. In the review by Murray et al. (2012), the focus is on the impact that co-morbidities have on stroke risk and outcome. For over 30 years a seasonal variation in the number of patients presenting with stroke has been noted, which led to the conclusion that 'infection may be important for the development of ischaemic stroke'. However, until recently, very few mechanistic studies have examined the relationship (McColl et al., 2007). Murray et al. discuss the choice of appropriate stroke model and highlight the roles for platelets and leukocytes that have been activated by the presence of the peripheral disease. In particular, the authors lament that, despite the widespread acceptance that a young healthy rat is not a good starting point for a model of stroke, the vast majority of studies never employ anything other than young healthy rats, and not obese, aged animals that would be more appropriate. However, the authors point out that the relationship between infection and outcome after stroke is not always straightforward and the review also touches on the phenomenon of protective preconditioning by inflammatory challenges. Following spinal cord lesions, the 'protective' effects of peripheral LPS administration have also been noted, which reinforce the mistake of making blanket statements about the detrimental effects of peripheral inflammation on the outcome of CNS injuries (Davis et al., 2005).

The second review on the interaction between the immune system and stroke contrasts with the first by considering the issue of post stroke immunosuppression. Here Brambilla and colleagues review the potential mechanisms that may underlie this phenomenon and end by concluding that while certain elements of the host immune response are undoubtedly suppressed by stroke, it is clear that the pattern is mixed and that the body adjusts to the ictus by augmenting some aspects of the immune repertoire while suppressing others. In particular, there is a redistribution and reduction in circulating lymphocyte populations and in the increase in the number of monocytes. However, the precise mechanism by which a CNS infarct reorganises the peripheral immune system very much remains a matter of speculation. Another phenomenon that has received very little attention is the matter of post stroke depression, which is also likely to involve a combination of central and peripheral cytokine expression.

We are aware that our choice of neuropathologies in this special issue has omitted reviews focused on Alzheimer's disease and Parkinson's disease. However, the contribution of inflammation to these pathologies has been dealt with extensively elsewhere (Barcia et al., 2011; Perry, 2012; Wyss-Coray and Rogers, 2012) and we were keen to highlight pathologies that have received less attention such as amyotrophic lateral sclerosis and the emerging field of inflammation in relation to brain metastasis. Evans et al. explore both the contribution of the glial response to

neurodegeneration in amyotrophic lateral sclerosis and the contribution of the acquired immune system. In particular, these topics are discussed in the context of the SOD-1 model of ALS (Beers et al., 2006). The SOD1 model, which carries a missense mutation in the gene for superoxide dismutase 1 (SOD1), is the most commonly used mouse model of ALS. We are often reminded that while the SOD-1 is a very good model of familial ALS, where there is a gain of function mutation in SOD-1, it is only relevant for 1–2% of ALS cases. However, within the review by Evans we see that the SOD-1 mutant animal is, in fact, an excellent model for studying the host response to chronic neurodegeneration. Unlike most murine models of Alzheimer disease for example, the SOD-1 mutant animal does exhibit neuronal cell death, and this occurs over a relatively long time course, which provides more scope suggest for the study of the influence of environment factors on outcome of the disease and neurodegenerative processes. The pathology displays both astrocyte and microglial activation and the neurodegeneration occurs along well-defined neuroanatomical pathways in a well characterised time course. Other pathologies, such as murine prion disease, are often argued to confer similar advantages for the study of chronic neurodegeneration. Their relative merits can be argued, such as the unknown contribution of the SOD-1 mutant on peripheral immune function in the ALS model, but there is no doubt that we need more models in which neurons die in a chronic manner with fewer of the confounds presented by the complex AD mutants, which are currently available.

If the role played by the host response to neurodegenerative disease appears unclear, this is even truer for the role of inflammation in brain metastasis. The similarities between leukocyte extravasation and the path that a tumour cell must take from the blood to seeding a secondary site has long been recognised (Opdenakker and Van Damme, 1992). However, it is clear that the CNS is a different compartment in terms of the growth substrate and the vasculature. Furthermore, the consequences of metastatic seeding in the brain are very severe. The presence of the blood brain barrier serves to exclude many therapies, especially high molecular weight antibodies, and the efflux transporters do a good job of removing therapy that does gain access. Hamilton et al. in their review in this issue discuss how inflammation has been viewed as an enabling characteristic of cancer (O'Leary et al., 2012), but also discuss how tumours need to avoid immune destruction as an emerging hallmark. Clearly, this seems counterintuitive, but it highlights the distinction between an immune response directed against the tumour or towards either another immunogen or a non-immune response after injury for example. We know that the blood–brain barrier (BBB) is not a barrier to cells (Bernardes-Silva et al., 2001), but it seems that though brain metastasis is not uncommon in humans there are relatively few cell lines that are able to establish brain metastases in experimental models. This suggests that the brain microenvironment must be relatively resistant to seeding and proliferation. Indeed, the authors point out that tumour cells seem to remain within the lumen of the cerebral blood vessels for longer than elsewhere in the body (Lorger and Felding-Habermann, 2010). While the process of tumour cell adhesion and extravasation is often likened to the way leukocytes cross the BBB, it is important to note that different leukocyte populations appear to cross the BBB by using distinct subpopulations of adhesion molecules and routes, such as via a paracellular or a transcellular route (Carman, 2009; Stamatovic et al., 2008). This may account, at least in part, for why certain cell lines do seed the brain and others do not. Thus it is clear from the review that plenty of work remains to be done to identify precisely which leukocyte population is resembled by any particular metastatic cell on its way into the brain, what adhesion molecules they use, and how the endothelium may contribute in the 'handshaking' period (Bolton et al., 1998). Sadly, it seems likely that each cell line will probably have its own unique characteristics, but this needs to be determined. The review also highlights the potential contribution of the host immune cell populations to tumour adhesion and proliferation and raises the possibility that tumour cells may piggyback on monocytes and platelets, for example, as they adhere to the activated endothelium. Work is still required to discover whether some of the regional variation in tumour metastasis sites might be attributable to differential adhesion molecule expression.

Having examined the impact of systemic immune system activation on existing brain pathology the second section in this special issue examines the effect of peripheral inflammation on brain function in the absence of any overt pathology or structural changes in brain architecture. However, it is clear that regional microglial activation is a feature of chronic stress paradigms in experimental models (Farooq et al., 2012), and post mortem examination of brains from suicide victims also reveals microglial activation suggestive of some remodelling processes (Steiner et al., 2008). In sickness behaviour induced by peripheral endotoxin administration, microglia have been shown to become 'activated' and display enhanced Translocator Protein (TSPO) binding (Hannestad et al., 2012). While the upregulation of the TSPO binding does not necessarily mean that a microglial cell is exhibiting a damaging phenotype it may be reflective of processes that are conserved both in chronic stress and in neurodegenerative disease. In each case, we suspect that much of the microglial activation is associated with the remodelling process such as synaptic scaling. Stellwagen has shown that homeostatic synaptic scaling in response to prolonged blockade of activity is mediated by TNF (Stellwagen and Malenka, 2006). However, the presence of activated microglia in these conditions raises the question of whether these microglia are primed in a similar manner to those found in prion, Alzheimer's and Parkinson's diseases and whether they might switch to a destructive phenotype in association with a sufficient peripheral challenge. It seems likely that these microglia will be more refractory to such challenges, but we do not know. The review of Jones and Thomson deals primarily with mood related illness, including major depression, bipolar disorder, and PTSD, and the contribution of the acquired and innate response to these conditions. It is clear from the review that while plenty of data is amassing to show that central cytokine production and the host immune response contributes to these conditions, there remains a lack of mechanistic data that bridges the gap between cytokine and the function of the neurotransmitter systems that are related to mood. In particular, there is still surprisingly little data about the nature of the neuronal cell populations, and their distribution, which are able to respond to the cytokines produced by microglia for instance (Fig. 1).

In the reviews by Stolp and by Depino the influence of maternal inflammation and perinatal inflammation on development and function in adulthood is considered. These reviews are related to that of Jones and Thomson in that the CNS response to a peripheral stressor is considered, but, here, Delpino and Stolp raise important questions relating to precisely how long-term changes in behaviour in offspring can be attributed to early life experience of infection or injury. At present we do not understand how pathologies as distinct as autism and schizophrenia can have such strong associations with similar infections during pregnancy. It seems likely that the timing of the inflammatory challenge will be important, but it remains unclear whether this predisposition is hard wired in altered neuronal circuitry or whether the outcomes are dependent on long-term alterations in the host inflammatory response. Stolp argues that brain architecture is subtlety altered, but it is clear from the review of Depino that postnatal exposure to inflammatory challenges can give rise to equally long-lasting effects and that the timing of this challenge is very important. The potential for the vertical transmission of the neurotrophic virus from the mother to the foetus is also considered, which, though not considered mainstream science by many, may contribute to adult neurological disorders and is, perhaps, more amenable to therapeutic intervention than targeting other element of the immunological response.

Following on from the consideration that infections during pregnancy may contribute to altered behaviour in adulthood, in the last section of our collection Bottasso et al. considers how a chronic peripheral infection can drive profound changes in energy metabolism and the 'consumptive' state, where the profound decrease in body weight remains unexplained. This review, unlike the others, considers how brain neuroendocrinology is affected by chronic infection as part of a preprogrammed homeostatic

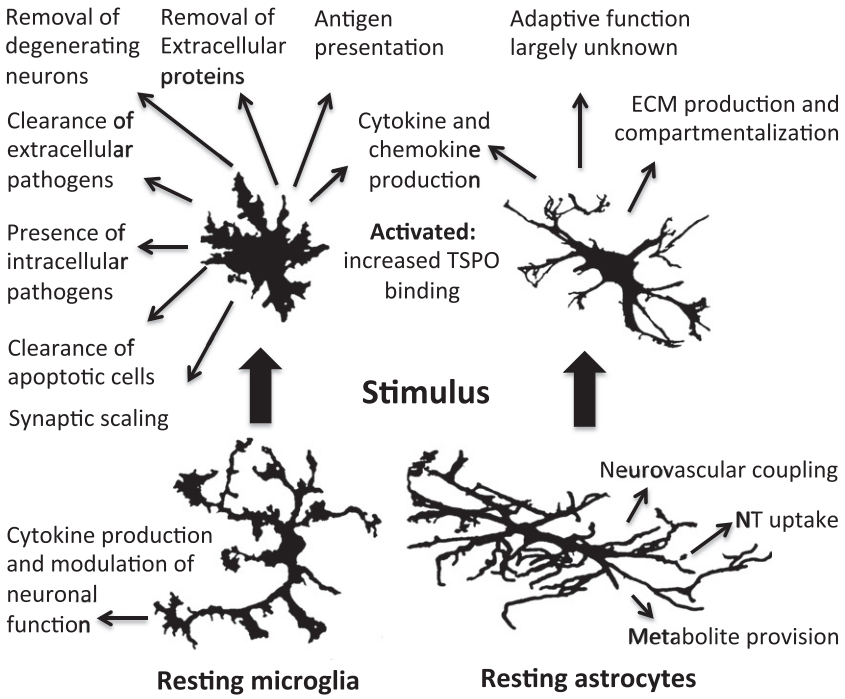

Fig. 1. Activation of microglia and astrocytes is associated with a change in cellular morphology and an increase in translocator protein (TSPO) binding as revealed by PET imaging. TSPO is present on the outer surface of mitochondrial membrane and an increase in binding is thought to reflect the increased energy demands associated with activation. However, microglial activation is associated with a diverse set of processes that may or may not be pathological. The function of astrocyte activation is largely unexplored.

response, which then appears to go wrong. In particular, Bottasso explores the tissue in the context of tuberculosis (TB), which now affects 14 million people worldwide. It is worth noting here that while cerebral TB is rare in the CNS (1% of case), it is perhaps one of the more dangerous forms of TB, which gives rise to a TB meningitis. It has been argued that the meningitis is caused by the rupture of caseating foci that develop around bacteria deposited brain parenchyma during the initial bacteremic phase (Thwaites and Schoeman, 2009). However, it remains unclear how the mycobacterium cross the BBB and, after invading the CNS, whether they populate the parenchyma of the brain, the vessel wall, or the endothelial cells lining the microvasculature. These are important issues, and are likely to become even more so as resistance to anti-tubercular therapy increases.

Considered together the reviews highlight the diverse pathologies that are now considered to have an inflammatory contribution. However, it will be immediately apparent that the use of the term inflammation in all these contexts does not properly encapsulate the diversity and complexity of the response. However, it remains clear that the activity of non-neuronal populations is greatly influenced by events in the periphery and vice versa and that the contribution of the host response to any given pathology is not static. We hope you enjoy these reviews.

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