Neuroscience 302 (2015) 103–111

REVIEW

NEUROINFLAMMATION IN ALZHEIMER'S DISEASE; A SOURCE OF HETEROGENEITY AND TARGET FOR PERSONALIZED THERAPY

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Abstract—Neuroinflammation has long been known as an accompanying pathology of Alzheimer's disease. Microglia surrounding amyloid plaques in the brain of Auguste D were described in the original publication of Alois Alzheimer. It is only quite recently, however, that we have a more complete appreciation for the diverse roles of neuroinflammation in neurodegenerative disorders such as Alzheimer's. While gaps in our knowledge remain, and conflicting data are abound in the field, our understanding of the complexities and heterogeneous functions of the inflammatory response in Alzheimer's is vastly improved. This review article will discuss some of the roles of neuroinflammation in Alzheimer's disease, in particular, how understanding heterogeneity in the individual inflammatory response can be used in therapeutic development and as a mechanism of personalizing our treatment of the disease.

This article is part of a Special Issue entitled: Inflammation in Nervous System Disorders.

Key words: microglia, amyloid, Alzheimer's, cytokines, phenotypes, inflammation.

Contents

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Abbreviations: Aβ, amyloid-beta; AD, Alzheimer's disease; ADAPT, Alzheimer's Disease Anti-inflammatory Prevention Trial; APP, amyloid precursor protein; ARG1, arginase 1; CAA, cerebral amyloid angiopathy; CSF, cerebrospinal fluid; ICAM1, intracellular adhesion molecule 1; IgG, immunoglobin G; IL, interleukin; IL-1Ra, IL-1 receptor antagonist; LPS, lipopolysaccharide; MIP1α, macrophage inflammatory protein 1 α; NSAIDs, non-steroidal anti-inflammatories; PET, Positron Emission tomography; TGFβ, transforming growth factor beta; TNFα, tumor necrosis factor alpha; VCAM1, vascular cell adhesion protein 1.

http://dx.doi.org/10.1016/j.neuroscience.2014.09.061

MICROGLIA

The key mediators of the neuroinflammatory response in the brain are its resident immune cells, microglia. In the early 1920s, Pio Del Rio Hortega made the first clear identification of microglia in the brain. Prior to this, however, glia were recognized by Nissl in 1899, who thought them to be neuroglia and hypothesized that they had abilities for migration and phagocytosis (reviewed by (Barron, 1995)). In their resting state, microglia extend ramified processes that survey the local micro-environment for invading pathogens, cellular debris and toxins (Streit et al., 1988). In response to these detrimental stimuli, microglia retract their extended filopodia to form a condensed ''ameboid'' structure (Lynch, 2009). This ''activated'' form governs a course of inflammation to follow suit with the objective of restoring homeostasis of the parenchyma and the eradication of pathogenic activity (Ousman and Kubes, 2012). In the last two decades, linked by myeloid derivation, the immunological response of microglia has been found to work in parallel in the central nervous system (CNS) to that of macrophages in the periphery (Colton et al., 2006). Therefore, many of the ideologies that define peripheral macrophage activity have been utilized to underpin the basis of neuroinflammation in the CNS. The term ''activated'' when referring to microglia has been synonymous with a cytotoxic, pro-inflammatory response in the brain.

ROLES OF MICROGLIA IN ALZHEIMER'S DISEASE (AD)

The presence of ''activated'' microglia were first described in the AD brain by Alois Alzheimer himself in his original report on Auguste D. in 1907. Alzheimer reported the presence of ''gliose'' associated with the plaques and tangles, which are the pathological hallmarks of AD (Alzheimer et al., 1995). Key studies by Streit and Perry in the late 1980s and early 1990s demonstrated that microglia responded to injury by becoming activated and

presenting cell surface antigens commonly associated with monocytes and macrophages (Hume et al., 1983; Perry et al., 1985; Streit and Kreutzberg, 1987; Streit et al., 1989; Bell et al., 1994). These findings, along with the gliosis observed in the AD brain, quickly led to the hypothesis that the microglia were contributors to the disease process. Key observations contributing to this hypothesis included elevated pro-inflammatory cytokine levels in the AD brain such as interleukin (IL)-1β, tumor necrosis factor alpha (TNFα) and IL-6, and *in vitro* studies showing that these pro-inflammatory cytokines led to neuronal toxicity and death (Akiyama et al., 2000). The autotoxic loop was proposed for neurodegenerative diseases such as AD, which hypothesized that the activation of microglia was initially a result of tissue injury and amyloid plaque deposition and this initial activation led to further tissue damage that would then result in further microglial activation and, thus, the process would continue (McGeer and McGeer, 1998a).

The hypothesis that microglial cells may have a beneficial effect in AD, as well as detrimental effects, emerged from several key *in vivo* studies. The first, in 2001, resulted from an attempt to initiate the autotoxic loop in an amyloid depositing mouse model. Lipopolysaccharide (LPS), a gram-negative bacterial cell-surface proteoglycan, was intracranially injected into the brains of aged APP/PS1 transgenic mice and, surprisingly, significantly lowered amyloid-beta (Aβ) deposition within 7 days (DiCarlo et al., 2001). Further, microglia took center stage when anti-Aβ immunotherapy emerged as a therapeutic approach to lower brain amyloid through the generation of anti-Aβ antibodies. First described in 1999, Schenk and colleagues hypothesized that a key mediator by which Aβ immunotherapy lowered Aβ was microglia-mediated phagocytosis through Fcγ receptor activation (Schenk et al., 1999). Later studies showed that microglial activation occurred in relation to amyloid reductions with both active and passive immunotherapy (Wilcock et al., 2001, 2004a). Both the immunotherapy studies and the LPS studies demonstrated that microglia could have a beneficial role in the neurodegenerative disease process, as well as a cytotoxic, detrimental role that had previously been hypothesized.

In contrast to the amyloid data, LPS injection into tau transgenic mice showed opposite effects. Intraparenchymal injection of LPS into the rTg4510 tau transgenic mice resulted in exacerbation of tau pathology 7 days later (Lee et al., 2010). This was determined by examining several phospho-epitopes of tau as well as Gallyas silver staining-positive neurofibrillary tangles. In addition to the standard microglial cell surface markers including CD45, this study identified additional markers of microglial activation stimulated by LPS; these were arginase 1 (ARG1) and YM1. The importance of these markers will be discussed later in this review. Additionally, LPS injection into the 3XTg mouse model of amyloid and tau pathology exacerbated the tau hyperphosphorylation (Kitazawa et al., 2005). These data suggest that tau and amyloid pathologies have opposite responses to the same inflammatory stimuli, in this case LPS. Whether this is the case for all inflammatory stimuli remains to be determined, however, these data should provide significant caution to the extrapolation of findings in amyloid depositing mice to the overall condition of AD.

Genetic overexpression of individual inflammatory cytokines has yielded data similar to those observed with LPS and anti-Aβ immunotherapy. Increased expression of transforming growth factor beta (TGFβ) by astrocytes results in reduced amyloid deposition and increased microglial activation in amyloid precursor protein (APP) amyloid depositing transgenic mice (Wyss-Coray et al., 2001). In addition, an interesting finding in this study showed that while parenchymal amyloid deposition decreased, vascular amyloid deposition (cerebral amyloid angiopathy; CAA) increased in a correlative manner. We observed a similar phenomenon with the anti-Aβ immunotherapy passive immunization studies, where we found increased CAA despite significantly decreased parenchymal amyloid deposition (Wilcock et al., 2004b). Additional studies with other monoclonal antibodies as immunotherapy have shown persistence of CAA, and many have demonstrated enhanced CAA-associated microhemorrhages (Wilcock and Colton, 2009). The data from Wyss-Coray et al. would suggest that inflammatory mechanisms may at least in part, be responsible for the shifted distribution of amyloid from the brain parenchyma to the cerebrovasculature.

TNFα and IL-1β are considered the major pro-inflammatory cytokines and are studied as classical markers of neuroinflammation. Individually, both have been implicated in an autotoxic loop, as both are capable of inducing cell death *in vitro* and *in vivo* (Good et al., 1996; Akassoglou et al., 1997; Thornton et al., 2006). Yet, when these pathways are targeted in amyloid depositing transgenic mice, the data show that these cytokine pathways may have some beneficial action by ameliorating amyloid deposition. One study that genetically deleted TNF receptors I and II in the 3XTg mouse model of amyloid deposition and tau pathology showed that blocking TNFα signaling actually increases amyloid deposition and tau pathology (Montgomery et al., 2011). Increased expression of IL-1β in the hippocampus of APP/PS1 amyloid depositing transgenic mice by genetic means resulted in reduced amyloid deposition and enhanced microglial activation (Shaftel et al., 2007). The author suggests that IL-1β-mediated activation of microglia is the mechanism for the reductions in amyloid deposition. However, in contrast to these studies, other studies have shown a clear relationship between IL-1β and neurodegeneration. In a similar way to the LPS studies, IL-1β has been shown to be responsible for tau hyperphosphorylation in an *in vitro* co-culture system of microglia and neurons (Li et al., 2003). Also, a positive correlation was observed when examining IL-1β levels compared to neurodegeneration in the APPV717F transgenic mice (Sheng et al., 2001). Therefore, while IL-1β may ameliorate amyloid pathology, it seems that the same pathways may also enhance tau pathology and neurodegeneration.

The contrasting data in different mouse models, cell culture models and stimulating agents clearly paints the picture of a complex process, one that cannot simply be defined as neuroinflammation.