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EXPERT REVIEWS

The promise of anti-inflammatory therapies for CNS injuries and diseases

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It remains controversial as to whether the inflammatory response plays a beneficial or detrimental role for cerebral tissue. There is substantial evidence that molecules of the innate immune reaction can be harmful to neurons and oligodendrocytes, whereas other observations indicate that inflammation is actually beneficial to recovery after injuries. One of the beneficial consequences of the immune reaction by microglia is the release of neurotrophic factors that have essential roles in brain homeostasis, neuroprotection and repair in cases of injury. Another important action of microglia is the clearance of cell debris and toxic proteins in order to prevent their accumulation in the extracellular space. Such beneficial effects of subsets of innate immune cells have to be taken into serious consideration in the planning of clinical trials using anti-inflammatory drugs for CNS diseases, which have failed so far. This very important subject has been discussed at the 13th Annual Meeting of the American Society for Experimental Neurotherapeutics in Bethesda, MD, USA.

Keywords: Alzheimer's disease • brain injuries • cytokines • gliogenesis • inflammation • innate immunity • microglia • Toll-like receptors

This lecture was presented at the 13th Annual Meeting of the American Society for Experimental Neurotherapeutics in Bethesda, MD, USA. This article includes the main message of the speakers of the session entitled 'Neuroinflammation'.

Although cytokines can be produced by and act on most cells of the CNS, microglia are thought to be the main cell type of the innate immune system in the brain. Microglia are present throughout the CNS; there are regions that are more populated than others and the white matter generally contains less microglia than the gray matter. They are highly ramified cells and their processes are very active and plastic, even during normal conditions [1]. Similar to macrophages, microglia express Toll-like receptors (TLRs), respond to TLR ligands and produce inflammatory mediators [2]. Several regulatory mechanisms are in place to avoid exaggerated immune responses by microglia during infection and trauma, including the production of anti-inflammatory cytokines by astrocytes and microglia, such as IL-10 and TGF-β, the activation of inhibitory signaling proteins such as IκBα, MKP and SOCS proteins within microglia, and the release of glucocorticoids by the adrenal gland. All of these events are critical in orchestrating the innate immune reaction in the brain in response to pathogen-associated molecular pattern molecules and damage-associated molecular pattern molecules.

Inflammation & neuronal injury

Acute neuronal injury is accompanied by microglia activation, *TLR2* gene expression and the induction of proinflammatory cytokines. Data supporting both a neuroprotective and a neurodestructive role for this response are numerous and have been reviewed extensively [3–8]. Such a dual effect of the immune reaction to injury and disease was highly debated at this meeting, especially in the session on neuroinflammation. Remyelination is reduced in TNF- and IL-1β-deficient mice [9–11] and mice deficient in TNF showed

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a dramatic exacerbation of neuronal damage following exposure to a source of nitric oxide [12]. Axonal regeneration and recovery of locomotor function are impaired in MyD88-deficient mice with peripheral nerve injury, and TLR2- or TLR4-deficient mice have slower recovery processes compared with wild-type mice [13]. Animals that received a single microinjection of TLR2 or TLR4 ligands at the site of sciatic nerve lesion had faster clearance of the degenerating myelin and recovered earlier than saline-injected control rats [13]. Locomotor recovery is also impaired in TLR2- or TLR4-deficient mice compared with control mice following spinal cord injury [14]. As discussed by Serge Rivest (Laval University, Québec, Canada), TLR-mediated responses can therefore regulate the responses required to efficiently eliminate cell debris and promote repair.

However, detrimental effects of TLR activation have been demonstrated in several animal models of acute injury, such as stroke, axotomy-induced neurodegeneration and administration of toxic molecules [15,16]. Annamaria Vezzani (Mario Negri Institute, Milan, Italy) presented data on the critical role played by IL-1 in animal models of epilepsy and she mentioned that a clinical trial is currently underway to test the effectiveness of IL-1 inhibition in a group of patients with epilepsy. Rivest mentioned that the synthesis of proinflammatory cytokines, microglia activation and leukocyte infiltration into the brain have been suggested to be important mechanisms in the pathogenic events that ultimately determine whether a stroke will result in reversible ischemic deficits or permanent damage. TNF and IL-1 mediate postischemic processes in the brain and inhibiting their actions is neuroprotective in animal models of stroke (reviewed in [3,4]). The impact of these cytokines on cerebral artery function may depend on the cell type that is primarily targeted or the subsequent immune reaction. IL-1 and TNF are rapidly produced in response to ischemic injury and they can contribute to the postischemic response either directly, by damaging endothelial cells, neurons and glial cells, or indirectly, via the recruitment of circulating leukocytes to the injured site. Indeed, the infiltration of monocytes, neutrophils and lymphocytes contributes to post-ischemic injury and their recruitment is largely dependent on the early release of proinflammatory molecules by resident cells [17]. However, this influx of immune cells can also act as a protective mechanism, as depletion of regulatory T (Treg) cells profoundly increased the level of delayed brain damage and of deteriorated functional outcome. In addition, Treg cell-derived IL-10 can suppress TNF and IFN-γ [18]. Therefore, this study suggests that Treg cells are important cerebroprotective modulators of postischemic inflammatory brain damage.

This mechanism may also be involved in the 'Yin and Yang' effects of inflammation for other CNS injuries and diseases. In this regard, Howard Gendelman (University of Nebraska Medical Center, NE, USA) presented data supporting a role of Tregs in the attenuation of Th17 cell-mediated neurodegeneration in a mouse model of Parkinson's disease [19]. As discussed by Bibiana Bielekova (NIH, MD, USA), these cells are believed to play a critical role in multiple sclerosis, at least in animal models of the disease. She raised interesting new concepts questioning the dogma that this autoimmune disease is largely attributed to the presence of proinflammatory cells.

Inflammation in Alzheimer's disease

Rivest raised serious concerns for the use of anti-inflammatory therapies in Alzheimer's disease (AD), which is a neurodegenerative disorder that represents the most significant cause of dementia in humans. Extracellular deposits of β-amyloid peptides (Aβ), often termed senile plaques, and formation of intracellular neurofibrillary tangles of hyperphosphorylated tau protein are the two principal hallmarks of this disease. It has been demonstrated that key receptors of the innate immune system are involved in the removal of Aβ from the brain. Indeed, the expression of CD14 is upregulated by microglia isolated from the brains of AD patients and a polymorphism of this receptor is associated with increased risks of this disease [20]. CD14 has been demonstrated to interact with the fibrillar $A\beta_{1-42}$ isoform and facilitates its phagocytosis [21]. It has also been reported that the Aβ load in the brain is modulated in part by TLR2 and TLR4 and that activation of TLR2, TLR4 and TLR9 increases the uptake of Aβ by microglia [22–24]. Scholtzova *et al.* have demonstrated that repeated systemic injections with the TLR9 agonist CpG-containing oligodeoxynucleotides produced a marked reduction in the cortical and vascular amyloid burden in a mouse model of AD [25]. This study also found a significant decrease in the levels of $A\beta_{1-42}$, $A\beta_{1-40}$ and Aβ oligomers in the brain, which was associated with improved cognitive functions. The expression of TLR3, TLR4, TLR5, TLR7, TLR8, TLR9 and TLR10 by macrophages is severely reduced in patients with AD following stimulation with Aβ compared with control subjects [26]. These data suggest that the expression of these innate immune receptors by macrophages and microglia in the CNS is a natural defense mechanism to prevent Aβ accumulation in the CNS.

Therefore, an important question that was discussed is why these receptors fail to remove Aβ in the CNS of patients with AD and in mouse models of this disease. It is possible that the phagocytic function of macrophages and microglia is decreased with disease progression or that the balance between Aβ production and clearance is abnormal during AD. Fiala *et al.* have reported that macrophages for most AD patients do not transport Aβ into endosomes and lysosomes or efficiently clear Aβ, although they can phagocytose bacteria [26]. It has been suggested by Rivest *et al.* that these cells are unable to recognize and eliminate Aβ owing to their low TLR2 expression level and that cognitive decline is markedly accelerated in a context of TLR2 deficiency [23].

Rivest presented evidence that stimulating the hematopoietic system may be a new therapeutic approach for the treatment of AD. In this regard, low macrophage colony-stimulating factor (M-CSF) levels were found in patients with presymptomatic AD or mild cognitive impairment, which together with low levels of other hematopoietic cytokines predicted the rapid development of the disease toward a dementia state 2–6 years later [27]. Exposure of mouse microglia to M-CSF *in vitro* enables the acidification of their lysosomes and subsequently, the degradation of

internalized Aβ [28]. Treatment of transgenic mice that spontaneously develop AD with M-CSF on a weekly basis prior to the appearance of learning and memory deficits prevented cognitive loss [29]. The treatment also increased the number of microglia in the parenchyma and greatly decreased Aβ levels in the brain. In addition, M-CSF treatment resulted in the stabilization of the cognitive decline state in transgenic mice that already had Aβ-meditated pathology.

Overall, these data indicate that the targeting of innate immune cells could have therapeutic potential for AD. On the other hand, a large number of studies have identified numerous detrimental effects of microglia and inflammatory molecules in AD. Gendelman presented similar evidence for Parkinson's disease and William Theodore (NIH, MD, USA) has developed new tools to image such responses during CNS diseases. Proinflammatory cytokines and prostaglandins are produced in the brain of mice with Alzheimer's-like disease and in patients with the disease. Inhibition of cytokine signaling (e.g., IL-1β) ameliorates disease progression in animal models of AD and administration of exogenous cytokines and COX-2 overexpression in the brain increase plaque formation and accelerate cognitive impairment. Anti-inflammatory drugs are beneficial in animal models of AD (reviewed in [7]). Moreover, initial clinical trials involving the treatment of susceptible patients with NSAIDs prior to the development of AD have suggested that inhibiting the immune response reduces the chance of developing the disease. However, recent data have shown that the administration of anti-inflammatory drugs to patients with AD not only failed to improve cognitive functions but was detrimental in some patients [30]. Actually, there is very limited evidence supporting a direct role of inflammatory pathways in this neurodegenerative disease, which may explain why treatments with anti-inflammatory drugs are not effective. It is tempting to propose that a defective innate immune system may allow Aβ accumulation in individuals with AD.

Conclusion & future directions

These data raise serious concerns for the general use of anti-inflammatory therapies in CNS injuries and diseases, and it is imperative to better understand the role of immune cells in the cerebral environment. New directions for research include the mechanisms involved in the activation profile, polarization, recruitment and differentiation of myeloid cells, which may play complementary and/or opposite roles. Very interesting novel concepts are emerging from such diversities between subsets of myeloid cells and manipulating their polarization is currently seen as the direction of future research for CNS disorders.

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References

1 Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma *in vivo*. *Science* 308(5726), 1314–1318 (2005).

2 Rivest S. Regulation of innate immune responses in the brain. *Nat. Rev. Immunol.* 9(6), 429–439 (2009).

3 Allan SM, Rothwell NJ. Cytokines and acute neurodegeneration. *Nat. Rev. Neurosci.* 2(10), 734–744 (2001).

4 Allan SM, Tyrrell PJ, Rothwell NJ. Interleukin-1 and neuronal injury. *Nat. Rev. Immunol.* 5(8), 629–640 (2005).

5 Glezer I, Simard AR, Rivest S. Neuroprotective role of the innate immune system by microglia. *Neuroscience* 147(4), 867–883 (2007).

6 Nguyen MD, Julien JP, Rivest S. Innate immunity: the missing link in neuroprotection and neurodegeneration? *Nat. Rev. Neurosci.* 3(3), 216–227 (2002).

7 Wyss-Coray T. Inflammation in Alzheimer disease: driving force, bystander or beneficial response? *Nat. Med.* 12(9), 1005–1015 (2006).

8 Wyss-Coray T, Mucke L. Inflammation in neurodegenerative disease – a double-edged sword. *Neuron* 35(3), 419–432 (2002).

9 Arnett HA, Mason J, Marino M, Suzuki K, Matsushima GK, Ting JP. TNFα promotes proliferation of oligodendrocyte progenitors and remyelination. *Nat. Neurosci.* 4(11), 1116–1122 (2001).

10 Herx LM, Rivest S, Yong VW. Central nervous system-initiated inflammation and neurotrophism in trauma: IL-1β is required for the production of ciliary neurotrophic factor. *J. Immunol.* 165(4), 2232–2239 (2000).

11 Mason JL, Suzuki K, Chaplin DD, Matsushima GK. Interleukin-1β promotes repair of the CNS. *J. Neurosci.* 21(18), 7046–7052 (2001).

12 Turrin NP, Rivest S. Tumor necrosis factor α but not interleukin 1β mediates neuroprotection in response to acute nitric oxide excitotoxicity. *J. Neurosci.* 26(1), 143–151 (2006).

13 Boivin A, Pineau I, Barrette B *et al.* Toll-like receptor signaling is critical for Wallerian degeneration and functional recovery after peripheral nerve injury. *J. Neurosci.* 27(45), 12396–12406 (2007).

14 Kigerl KA, Lai W, Rivest S, Hart RP, Satoskar AR, Popovich PG. Toll-like receptor (TLR)-2 and TLR-4 regulate inflammation, gliosis, and myelin sparing after spinal cord injury. *J. Neurochem.* 102(1), 37–50 (2007).

15 Kilic U, Kilic E, Matter CM, Bassetti CL, Hermann DM. TLR-4 deficiency protects against focal cerebral ischemia and axotomy-induced neurodegeneration. *Neurobiol. Dis.* 31(1), 33–40 (2008).

16 Tang SC, Lathia JD, Selvaraj PK *et al.* Toll-like receptor-4 mediates neuronal apoptosis induced by amyloid β-peptide and the membrane lipid peroxidation product 4-hydroxynonenal. *Exp. Neurol.* 213(1), 114–121 (2008).

17 Wang Q, Tang XN, Yenari MA. The inflammatory response in stroke. *J. Neuroimmunol.* 184(1–2), 53–68 (2007).

18 Liesz A, Suri-Payer E, Veltkamp C *et al.* Regulatory T cells are key cerebroprotective immunomodulators in acute experimental stroke. *Nat. Med.* 15(2), 192–199 (2009).

19 Reynolds AD, Stone DK, Hutter JA, Benner EJ, Mosley RL, Gendelman HE. Regulatory T cells attenuate Th17 cell-mediated nigrostriatal dopaminergic neurodegeneration in a model of Parkinson's disease. *J. Immunol.* 184(5), 2261–2271 (2010).

20 Combarros O, Infante J, Rodriguez E *et al.* CD14 receptor polymorphism and Alzheimer's disease risk. *Neurosci. Lett.* 380(1–2), 193–196 (2005).

21 Liu Y, Walter S, Stagi M *et al.* LPS receptor (CD14): a receptor for phagocytosis of Alzheimer's amyloid peptide. *Brain* 128(Pt 8), 1778–1789 (2005).

22 Chen K, Iribarren P, Hu J *et al.* Activation of Toll-like receptor 2 on microglia promotes cell uptake of Alzheimer disease-associated amyloid β peptide. *J. Biol. Chem.* 281(6), 3651–3659 (2006).

23 Richard KL, Filali M, Prefontaine P, Rivest S. Toll-like receptor 2 acts as a natural innate immune receptor to clear amyloid β 1–42 and delay the cognitive decline in a mouse model of Alzheimer's disease. *J. Neurosci.* 28(22), 5784–5793 (2008).

24 Tahara K, Kim HD, Jin JJ, Maxwell JA, Li L, Fukuchi K. Role of Toll-like receptor signalling in Aβ uptake and clearance. *Brain* 129(Pt 11), 3006–3019 (2006).

25 Scholtzova H, Kascsak RJ, Bates KA *et al.* Induction of Toll-like receptor 9 signaling as a method for ameliorating Alzheimer's disease-related pathology. *J. Neurosci.* 29(6), 1846–1854 (2009).

26 Fiala M, Liu PT, Espinosa-Jeffrey A *et al.* Innate immunity and transcription of MGAT-III and Toll-like receptors in Alzheimer's disease patients are improved by bisdemethoxycurcumin. *Proc. Natl Acad. Sci. USA* 104(31), 12849–12854 (2007).

27 Ray S, Britschgi M, Herbert C *et al.* Classification and prediction of clinical Alzheimer's diagnosis based on plasma signaling proteins. *Nat. Med.* 13(11), 1359–1362 (2007).

28 Majumdar A, Cruz D, Asamoah N *et al.* Activation of microglia acidifies lysosomes and leads to degradation of Alzheimer amyloid fibrils. *Mol. Biol. Cell* 18(4), 1490–1496 (2007).

29 Boissonneault V, Filali M, Lessard M, Relton J, Wong G, Rivest S. Powerful beneficial effects of macrophage colony-stimulating factor on β-amyloid deposition and cognitive impairment in Alzheimer's disease. *Brain* 132(Pt 4), 1078–1092 (2009).

30 Martin BK, Szekely C, Brandt J *et al.* Cognitive function over time in the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT): results of a randomized, controlled trial of naproxen and celecoxib. *Arch. Neurol.* 65(7), 896–905 (2008).