Published in final edited form as:
CNS Neurol Disord Drug Targets. 2010 April ; 9(2): 129–131.

Inflammation, Immunity, and Alzheimer's Disease

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Abstract

Few topics in the field of Alzheimer's disease (AD) research have brought about the level of excitement and interest as the role of inflammation and immunity in the pathobiology and treatment of the disease. In this special issue of the journal, experts in the field give their views on how inflammatory processes and the immune system intersect- at both the etiological and treatment levels- with disease biology. Collectively, nearly three decades of work are covered in this special issue, beginning with the first epidemiologic studies that showed an inverse risk relationship between AD and use of non-steroidal anti-inflammatory drugs, and ending with "immunotherapy" approaches and recent studies examining the roles of innate immune cells, including microglia and peripheral mononuclear phagocytes in AD. Despite considerable work in this area, many important questions remain concerning the nature and timing of immune/inflammatory responses in the context of AD, and at what point and how to therapeutically intervene.

Alzheimer's disease (AD), hallmarked by progressive loss of pneumonic and higher cortical functions and presence at autopsy of amyloid plaques and neurofibrillary "tangles," is the most common form of dementia in the elderly. Numerous lines of genetic, epidemiologic, and pathologic evidence point to the amyloid precursor protein and its proteolytic product, amyloid β-peptide (Aβ), as central players in AD etiology [1]. While plaques and tangles are most often associated with the disease, it is interesting to note that over a century ago Alois Alzheimer himself described a third pathological feature in the historical first case of Auguste D., a female presenting with dementia [2]. What he termed "*gliose*," we now refer to as "gliosis" or inflammation of the brain's support cells known as glia. For decades after Alzheimer's original case report, many believed that gliosis (or brain inflammation) was an epiphenomenon with little relevance to AD etiology. We now know not only that gliosis and brain inflammation are much more integral to AD pathoetiology than once appreciated, but also that targeting inflammation and the immune system represent promising therapeutic approaches for the disease.

This "hot topic" issue opens with a critical review by **Christine Szekely** and **Peter Zandi** of the epidemiologic evidence – both in support of and against – use of non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment or prevention of AD. In the early 1990s, a

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number of observational studies reported an inverse risk relationship between NSAID use and AD. In many of these studies, the patient population consisted of individuals who were using NSAIDs to treat arthritis, and so it was assumed that arthritis was a surrogate for NSAID use. While ~25 observational studies have consistently shown that NSAID use is associated with lower incidence of AD, the randomized controlled trial literature does not generally support this notion. Unfortunately, the only primary prevention trial to test whether NSAIDs were beneficial, the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT), was prematurely halted after only 2 years of exposure and limited follow-up due to cardiovascular safety concerns of selective cyclooxygenase (COX)-2 inhibitors. Because of this, interpretation of results from this trial has been complex. The authors present five compelling explanations for why the observational studies and randomized controlled trials are at odds, and attempt a synthesis of the epidemiologic evidence [3].

While the above authors review the epidemiologic evidence on NSAIDs and AD, **Greg Cole** and **Sally Frautschy** focus on mechanisms of NSAID action in AD. The authors begin by presenting a comprehensive synopsis of the NSAID-AD rodent model literature, which generally shows a reduction in cerebral amyloidosis following treatment with numerous COX-1- or COX-2-selective NSAIDs. They move on to discuss the ADAPT trial results and evidence from animal models and laboratory studies showing a direct Aβ-lowering effect of a subclass of NSAIDs *via* modulation of presenilin-1/γ-secretase activity. These authors raise our awareness that based on largely null results from selective COX-2 NSAID clinical trials, COX-1 may be a more viable NSAID target. Further, they suggest that the primary mechanism of chronic NSAID use in the context of AD is to reduce amyloid accumulation and thereby delay onset of the disease. Finally, they review important studies that show an apolipoprotein E4-dependent NSAID protective effect, and suggest reasons related to brain inflammation that may explain this result [4].

Jun Tan and colleagues carry on the theme of brain inflammatory response pathways by focusing on the pro-inflammatory CD40-CD40 ligand (CD40L) dyad in the pathogenesis and potential treatment of AD. The authors open by introducing the CD40 receptor and its cognate ligand, CD40L, and submit that most of our knowledge of this pair comes from peripheral immune cells. They review studies showing that CD40-CD40L interaction on microglia enables activation of these cells in response to soluble Aβ peptides, and that inhibition of the CD40 pathway by genetic or pharmacologic means mitigates AD-like pathology in transgenic mouse models of the disease. They also cover recent studies suggesting that elements of the CD40 pathway may represent valuable biomarkers for AD. Finally, they review four different therapeutic strategies for AD that impact the CD40-CD40L pathway, including statins, plant-derived polyphenols known as flavonoids, human umbilical cord blood cells, and Aβ vaccine “immunotherapy” [5].

Microglia are generally regarded as the key brain-resident innate immune cells that are responsible for directing brain inflammatory responses. **Shweta Mandrekar-Colucci** and **Gary Landreth** present a timely and thought-provoking review on the mechanisms by which microglia referee neuroinflammatory and neuroprotective responses. The authors begin by highlighting the dynamic roles that microglia play in the healthy brain, and discuss how microglia respond to amyloid plaques in brains of AD patients and AD model mice. They classify different mechanisms of microglial activation, including *in vivo* intrinsic regulation, Aβ phagocytosis, and microglial Aβ receptor complex. They move on to consider the role of Toll-like receptors, innate immune pattern recognition receptors that are tuned to recognize pathogens and danger-associated molecular patterns, in microglial inflammation and Aβ clearance. The authors also critically review the role of the protein complement system in microglial Aβ clearance, and conclude by covering recent evidence that peripheral

mononuclear phagocytes infiltrate into the brain and may play a key role in restricting cerebral amyloid [6].

The provenance of brain microglia in AD – whether of central or peripheral origin – is explored by **Susanne Hickman** and **Joseph El Khoury**. The authors begin by reviewing histological evidence showing that microglia are clustered in and around Aβ plaques in AD patients, and that Aβ phagocytic microglia are sometimes found in AD patient brains, especially in the rare comorbidity of AD with stroke. While the jury is still out on whether such Aβ phagocytosis truly occurs in AD and is representative of a *bona fide* Aβ clearance pathway, recent evidence indicates that deficiency in the chemokine receptor CCR2 leads to impaired recruitment of mononuclear phagocytes in Tg2576 AD model mice concomitant with increased cerebral amyloid burden. Conversely, increased recruitment of these cells to brains of AD mice, either by constitutive expression of the cytokine interleukin-1 or by blocking innate immune transforming growth factor-β-Smad 2/3 signaling, results in restriction of cerebral amyloidosis. These and other results suggest that interaction of microglia/mononuclear phagocytes with Aβ deposits is a central event in the pathobiology of AD. The authors go on to describe various experimental strategies, including generation of chimeric mouse models expressing green fluorescent protein in the bone marrow compartment, that in principle allow for discriminating peripheral from CNS-resident mononuclear phagocytes. Interestingly, trafficking of peripheral mononuclear phagocytes to the CNS is not restricted to AD, but rather seems to be a general phenomenon in many neuroinflammatory diseases. The authors conclude by presenting an in-depth discussion of the various chemokine pathways that contribute to CNS recruitment and activation of mononuclear phagocytes [7].

Carol Colton and **Donna Wilcock** continue on with the theme of microglial activation, but focus rather on the concept of microglial activation states. While it was once thought that microglial “activation” was a single phenotype, it is now being appreciated that many different “flavors” of microglial activation exist, with some forms being neurotoxic and others, neuroprotective. The authors begin by relating microglial morphology with function, and then build a general framework of various forms of microglial activation based on functional properties. They broadly classify microglial activation into: “classical activation,” which is associated with production of pro-inflammatory cytokines that may promote bystander damage; “alternative activation,” which is associated with expression of genes that promote tissue repair; and finally, “acquired deactivation,” which is typified by inhibition of pro-inflammatory cytokine responses. In addition to detailing the functional properties of various microglial activation states, the authors describe phenotyping methods that allow for identification of discrete forms of microglial activation. These authors raise awareness that the functional outcome of microglial activation depends on initiating contextual cues leading to specific forms of innate immune activation [8].

One of the central questions concerning microglial activation states and brain inflammatory response pathways that have apparently gone awry in AD patient brains is how to re-balance them. **Milan Fiala** presents a thought-provoking view of various therapeutic strategies designed to do just that. He begins by describing immune surveillance of the CNS by leukocytes, and then explains what he terms “the immune double-default” present in AD patient brains, characterized by increased neuroinflammation but defective Aβ phagocytosis. Concomitantly, a number of pro- and anti-inflammatory cytokines are dysregulated in AD patients, and there is an increase in incompetent memory T cells and a corresponding decline in macrophages in these patients. The author suggests a number of interventions to re-balance inflammation and phagocytosis, including exercise, plant-derived bioactive dietary supplements, antioxidants, and vitamin supplements [9].

While the above therapeutic approaches focus on dietary supplements and exercise, a more radical AD therapeutic has been so-called Aβ "immunotherapy," broadly defined as harnessing the immune system to recognize and limit cerebral amyloid. **Cindy Lemere** and colleagues provide a comprehensive review of studies in this area, beginning with a definition of "active" and "passive" forms of Aβ immunotherapeutics. The authors describe positive results of both immunotherapies on reducing cerebral amyloid and ameliorating behavioral impairment in mouse models of AD. Further, active Aβ immunization has been shown to modulate plasma and cerebrospinal fluid Aβ levels in non-human primates. However, the first clinical trial of active Aβ immunotherapy, AN-1792, was prematurely halted due to aseptic meningoencephalitis in ~6% of AD patients who received the vaccine, despite seemingly beneficial effects on reduced cerebral amyloid in a subset of patients who developed high-titre Aβ antibodies. The authors go on to review other AD immunotherapeutic strategies that are in various stages in the pipeline, from pre-clinical studies in animal models to early developmental clinical trials. These authors conclude by describing potential mechanisms that underlie Aβ immunotherapy, including microglial Aβ phagocytosis, antibody-mediated neutralization of Aβ toxicity, and Aβ clearance by the "peripheral sink" hypothesis [10].

Finally, **David Cribbs** offers a different take on Aβ immunotherapy, and makes a compelling case for Aβ DNA-based vaccination as a viable AD prevention strategy. His review opens by justifying Aβ as a primary target for AD therapy, and then transitions into pre-clinical studies in transgenic AD model mice that show beneficial effects of active and passive immunization. The author presents an interesting view of the Elan/Wyeth AN-1792 trial, and makes a good argument that use of the T helper type 1-promoting adjuvant, QS-21, and the polysorbate 80 vaccine solubility modification conspired to provoke an auto-aggressive T cell response that led to severe brain inflammation and aseptic meningoencephalitis in a subset of vaccinated AD patients. Other challenges facing Aβ immunotherapy include immunosenescence in elderly individuals, the need to focus on disease prevention as opposed to active treatment, and the problem of adjuvant choice. The author critically considers advantages of DNA-based as opposed to peptide-based Aβ vaccines, including ability to induce long-lasting immune responses and the relatively simple production and high stability of these vaccines. Finally, the author explores various DNA vaccine delivery options to efficiently introduce therapeutic doses of Aβ DNA vaccines [11].

In closing, the articles in this special issue provide penetrating and though-provoking views of broad impact to AD research. Collectively, th ese comprehensive reviews raise numerous questions with wide-ranging implications for the field of AD neuroimmunology.

Acknowledgments

The editor is supported by an NIH/NIA "Pathway to Independence" award (5R00AG029726-03 and 5R00AG029726-04), and is the inaugural holder of the Ben Winters Endowed Chair in Regenerative Medicine. The editor would like to extend a warm thanks to Drs. Kavon Rezai-Zadeh (Cedars-Sinai Medical Center), David Morgan (University of South Florida), and Christine A. Szekely (Cedars-Sinai M edical Center) for assistan ce with reviewing the manuscripts in this special issue.

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