Editorial

Are Inflammatory Alterations a Cause or Consequence of Neurodegeneration in Alzheimer's Disease?

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Numerous inflammatory mediators have been identified in Alzheimer's disease (AD) brains but not detected in non-demented elderly individuals selected as controls. Emerging evidence suggests that neuroinflammation is involved in the pathogenesis of AD. Recently, there have been interesting reports suggesting the contribution of interleukin (IL)-2 [1], IL-10 [2,3], IL-33 [4], colony-stimulating factor 1 (CSF1) [5], and tumour necrosis factor α (TNFα) [6,7] to AD pathogenesis, and their potential therapeutic uses in AD have been suggested. Interestingly, several anti-TNFα agents and TNFα-modulating agents including infliximab, etanercept, thalidomide, and minocycline attenuated amyloid-β peptide (Aβ) deposition, behavioural impairments, and inflammation in AD animal models [8], and perispinal, but not subcutaneous, delivery of etanercept to AD patients exhibited a significantly rapid and sustained cognitive improvement [9]. Furthermore, inflammasomes, which cleave precursors of IL-1β and IL-18 to generate their active forms, play an important role in AD pathogenesis [10], as their activation in the microglia by Aβ triggers neuroinflammation [11].

Therefore, anti-inflammatory strategies have been proposed to have beneficial disease-modifying effects on AD. AD therapeutics based on the amyloid hypothesis have shown limited efficacy in patients, suggesting other aspects of AD pathogenesis contributing to neuronal death and cognitive decline. It is well known that some mismatch individuals, referred to as high pathology control (HPC) [12-14], exhibit high levels of Aβ accumulation in their brain without significant cognitive decline or neuronal loss. One important difference between the mismatches and AD brains is that the mismatches exhibit a reduced level of neuroinflammation [7]. Neuroinflammation has been proposed to be one of the candidate mechanisms involved in the initiation and propagation of synaptic loss, leading to further progression of AD pathology with manifestation of dementia [12]. The significant contribution of inflammation to AD pathogenesis may partly depend on the protein function altered by sequence variants of the immune-related genes, such as *CR1*, *TREM2*, *CD33* and *HLA-DRB5-HLA-DRB1*, which were revealed by recent genome-wide association studies to be associated with an increased risk for the development of AD. In particular, the R47H variant of *TREM2* is the first gene to be identified with a moderate risk effect on the disease to a similar extent as that observed for the *APOEε4* allele, since the association of the *APOEε4* was established for AD [15,16]. The *TREM2* gene encodes the triggering receptor expressed on myeloid cells 2 protein. In the brain, TREM2 is preferentially expressed in microglia.

Aβ deposits, neurofibrillary tangles (NFTs), and neuronal degeneration are characteristic of AD and are the most likely sources of inflammation in AD brains. In contrast, Aβ and Aβ precursor protein (APP) are regulated by inflammatory mediators. Neuroinflammation causes neuronal damage in AD and is now thought to possibly contribute to AD pathogenesis rather than being a consequence of emerging senile plaques, NFTs, and neurodegeneration. In fact, long-term non-steroidal anti-inflammatory drug (NSAID) users were prospectively demonstrated to have a lower risk of AD than non-NSAID users [17] and retrospective studies have shown that treating rheumatoid arthritis with anti-inflammatory medications may reduce the risk of AD [18]. If inflammatory alterations are primary to AD pathologic processes that occur before neuronal damage and dementia, then anti-inflammatory therapies using NSAIDs will prevent cognitive impairment in AD. However, the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) and its follow-up study (ADAPT-FS) did not support the use of NSAIDs for AD prevention among dementia-free elderly individuals with a family history of AD [19].

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A longitudinal positron emission tomography (PET) imaging study with ^{11}C-deuterium-L-deprenyl (^{11}C-DED), a selective monoamine oxidase B antagonist that labels activated astrocytes, in asymptomatic carriers of autosomal dominant AD demonstrated that astrocytes had already been activated when amyloid deposition was first observed using ^{11}C-Pittsburg Compound B (PIB), an amyloid tracer. This suggests that astrocytic inflammatory responses are implicated in the early stages of AD pathology [20]. On the other hand, a soluble TREM2 (sTREM2) in the cerebrospinal fluid was demonstrated to increase early in the progression of autosomal dominant AD; that is, before the expected cognitive decline, but after changes in Aβ and tau–measured by PIB-PET imaging, CSF Aβ, and CSF tau–have already begun. This suggests that microglial activation occurs after the occurrence of amyloidosis and neuronal injury [16].

Are inflammatory alterations a cause or consequence of neuro-degeneration in AD? This issue has been controversial. To address this issue, investigation of alterations in a group of molecules related to the metabolism of APP, Aβ, tau, and inflammation, using HPC brains should be attempted and compared with those of AD and healthy elderly controls. Non-demented individuals with AD pathology or aforementioned "mismatch individuals", referred to as HPC individuals, are considered an intermediate subset between AD and healthy elderly controls. The data obtained from this attempt are very revealing and clarify the specific mechanisms that enable some elderly individuals harboring high levels of Aβ to evade cognitive decline [12-14].

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