Neuroinflammation in Alzheimer's disease-A Review

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Abstract

Alzheimer's disease is the most common neurodegenerative disease affecting the ageing population. The two pathological hallmarks most prominently detected in brain tissue samples are neurofibrillary tangles and amyloid plaques. However, neuroinflammatory markers like TNFα, interleukins and cytokines are also pronounced in the alzheimer's disease brain. This review focusses on the mechanisms underlying neuroinflammation and rodent models which can be used to establish in vivo neuroinflammation.

Keywords: Alzheimer's disease, oxidative stress, chemokines, caspases

Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disease and is the most common cause of dementia. AD is characterized by two pathological hallmarks the senile plaques, which are mainly composed of extracellular deposits of amyloid-β (Aβ), and neurofibrillary tangles, which consist of intracellular aggregates of aberrantly phosphorylated tau protein. Inflammation is a prominent feature in AD. It has been proposed that aging has an effect on the function of inflammation in the brain, thereby contributing to the development of age-related diseases like AD.

The role of inflammation in AD has been supported by genome-wide association studies that have identified genes involved in inflammation that are associated with increased risk of developing AD [1,2]. The important role of neuroinflammation is supported by findings that genes for immune receptors, including

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TREM2 [3] and CD33 [4,5] are associated with Alzheimer's disease. Generally inflammatory response in usually considered as a double-edged sword. It is a defensive mechanism aimed at eliminating injurious stimuli and restoring tissue integrity. However, inflammation may become a harmful process when it becomes chronic. Chronic activation of the inflammatory response in AD produces pro-inflammatory cytokines, prostaglandins and reactive oxygen species that exacerbate Aβ deposition and induce neuronal dysfunction [6].Clinicopathological studies suggest that neuroinflammation, and in particular microglial activation, is an early event in AD pathology. The volume of tissue occupied by microglia, the brain resident macrophages, increases with severity of dementia, but peaks in moderately affected cases [7]. The volume density of microglia is already increased in early pathological stages of AD and in cognitively normal subjects with frequent presence of plaques and tangles.

It is becoming increasingly evident that neuroinflammation plays a crucial role in the development and progression of many diseases of the central nervous system (CNS). Hence, this review aims at discussing the pathogenesis of inflammation in AD, the inflammatory biomarkers and the rodent models that can be used to study the role of neuroinflammation and their mediators.

Mechanisms of neuroinflammation in AD

Oxidative stress as a driver of neuroinflammation

Oxidative stress can be viewed both as a cause, and as a consequence, of neuroinflammation. To consider oxidative stress as a causal or mechanistic factor in the onset and progression of a neuroinflammatory cycle, one needs to consider the role of ROS (reactive oxygen species) and RNS (reactive nitrogen species) as signal transduction mediators or second messengers. TNF-α (tumor necrosis factor α) mediated production of intracellular ROS, which might occur through ceramide-triggered mitochondrial ROS leakage [8]. Cytokine-triggered ROS production through NADH oxidases (NOX) is another, ubiquitous mechanism often implicated for inflammogen-triggered intracellular ROS generation. Nitric oxide is generated by astrocytes and microglia through the high-yield inducible nitric oxide synthase (iNOS) and in smaller transient bursts through neuronal nNOS isoforms.

Neuroinflammatory Markers
Cytokines

Chronic neuroinflammation includes longstanding activation of microglia and subsequent sustained release of inflammatory mediators. The sustained release of cytokine works to initiate the inflammatory cycle, activating microglia, promoting their proliferation, and further release of inflammatory factors. Cytokines are known to be the major regulators of neuroinflammation, so that their CSF and blood levels reflect many characteristics of this process and potentially constitute novel biomarkers. Common cytokines, which regulate inflammatory response, include interleukins (ILs), interferons (IFNs), and chemokines. In AD, signs of chronic neuroinflammation driven by persistent microglia activation and pro-inflammatory cytokine release may induce a cascade of neurotoxic changes leading to disease progression and development [9].

Evidence suggests that the proinflammatory environment present in the brains of patients with Alzheimer's disease and in transgenic mouse models of cerebral amyloidosis leads to extensive degeneration of brain tissue. For example, risk for conversion from mild cognitive impairment to the dementia stage of Alzheimer's disease is increased in patients with elevated concentrations of the proinflammatory cytokine TNF-α and decreased concentrations of anti-inflammatory TGF-β in the CSF. Interleukin-1β, TNF-α, and other cytokines might impair neuronal function even before leading to structural changes, as shown by suppression of long-term potentiation (LTP) of synaptic transmission. Several interactions, and increased expression of additional cytokines, chemokines, and innate immune receptors, favour an M1-like activation state in Alzheimer's disease. Elevated levels of several cytokines (TNF-alpha, TGF-beta) and interleukins have been associated with the pathology, and evidence suggests that immunotherapy can be a promising intervention strategy [9].

Chemokines

Chemokines have been suggested to regulate microglial migration to areas of neuroinflammation, thereby enhancing local inflammation in Alzheimer's disease. In AD, up-regulation of CCL2, CCR3, and CCR5 in reactive microglia has been reported, whereas CCL4 has been detected in reactive astrocytes near Aβ plaques [10]. In vitro, Aβ leads to generation of CXCL8 (also known as interleukin 8), CCL2, CCL3, and CCL4 in human macrophages and astrocytes, and microglia cultured from autopsies of patients with Alzheimer's disease revealed increased

expression of CXCL8, CCL2, and CCL3 after experimental exposure to Aβ [11].

Caspases

Caspases are a family of intracellular proteases that are key mediators of apoptosis and inflammation. Of the inflammatory caspases, the catalytic activity of caspase 1 is tightly regulated by signal-dependent autoactivation within inflammasomes, which mediate caspase 1 autocatalytic activation and subsequent cleavage of precursors of interleukin 1β and interleukin 18 into bioactivecytokines. Aβ fibrils can activate NRLP3 inflammasomes via lysosomal damage in mouse microglia [12].Increased concentrations of active caspase 1 is detected in the brains of patients with Alzheimer's disease and APP/PS1 mice. Additionally, APP/PS1 mice deficient in NLRP3 or caspase1 are mostly protected from spatial memory impairment, loss of hippocampal synaptic plasticity, associated behavioural disturbances associated with Alzheimer's disease. The stimulation of microglia with various proinflammatory mediators led to orderly activation of apoptotic caspase 8 and caspase 3/7. Activated caspase 3 modulates NF-κB activation via PKCδ and increases production of neurotoxic proinflammatory mediators, such as interleukin 1β, TNFα, and nitric oxide. Inhibition of these caspases hindered microglia activation and neurotoxicity [13].

Rodent models of neuroinflammation

In conventional transgenic animal models of AD, neuroinflammation is mainly known as a secondary response to sustained Aβ overproduction and deposition. It includes microglial activation and variable involvement of the complement system and production of cytokines [14]. An ideal disease model should recapitulate causes, lesions, and symptoms in a chronological order similar to the actual disease [15]. A faithful model to the inflammation

hypothesis of AD should be an aged animal that recapitulates early chronic neuroinflammation prior to hyperphosphorylation of tau and Aβ plaque deposition. In rats, a neuroinflammatory process lasting more than 7 days is considered chronic neuroinflammation; and rodents older than 22 months are considered senescent [16].

Immune challenge-based models

Chronic neuroinflammation was modeled through continuous infusion of picomolar concentrations of LPS into the fourth ventricle of adult rats. A widespread activation of microglia was detected 2 days after the initiation of LPS infusion. Within 2 weeks after the cessation of LPS infusion, microglial activation decreased in most brain areas barring the hippocampus, and after the following 2 weeks, inflammation was mainly localized in the hippocampus [17]. Furthermore, MRI scans showed shrinkage of the temporal lobe and enlargement of the lateral ventricles. Electron microscopic studies showed impaired protein synthesis in hippocampal neurons of LPS-injected animals. Moreover, neuronal loss and impairment of long-term potentiation were reported in the entorhinal cortex and the dentate gyrus of the hippocampus respectively, altogether explaining the decline in spatial memory. In this model, LPS-induced neuroinflammation was time dependent (maximal within 4 weeks of infusion) as well as cell and region specific (microglia in hippocampus) [18].

Other groups have provided evidence of exacerbated AD related protein pathology such as increased Aβ production through enhanced β-secretase activity in APP sweTg and tau hyperphosphorylation in 3xTg-AD mice following LPS injection [19]. However, wild-type animals injected with LPS showed no increased Aβ deposition in the time course of 3 months. Another explanation for the lack of Aβ deposition in LPS-injected animals was

proposed by DiCarlo et al. by showing a reduction of established Aβ plaques after intrahippocampal LPS injection through stimulation of Aβ clearance [20].

Neurotoxin-induced models

These include streptozotocin, okadaic acid and colchicine induced models of neuroinflammation. Peripheral injection of the glucosamine-nitrosurea compound streptozotocin (STZ) selectively damages pancreatic β cells after being taken up via the glucose transporter SLC2A2. Thus, repetitive intraperitoneal injection of STZ is an established animal model of diabetes mellitus. Interestingly, after STZ-mediated induction of diabetes, rodents display impaired neuronal plasticity and learning deficits. A single ICV injection of 1 or 3 mg/ml STZ in rats has been shown to cause chronic neuroinflammation, dilation of the ventricles, and atrophy of the septum with reduction of neuronal cell counts. Both STZ concentrations cause these effects; however, they are more pronounced at 3 mg/ml [21]. When administered to transgenic models of AD, ICV-STZ was shown to exacerbate neuroinflammation, cognitive deficits, plaque pathology, and tau hyperphosphorylation [22], indicating that STZ renders the brain more susceptible to the pathological hallmarks of AD. Similar exacerbating effects were observed when STZ was administered intraperitoneally to AD transgenic mice [23].

A comparable model to STZ-induced neuroinflammation is okadaic acid (OKA)-induced neuroinflammation. OKA is a major polyether toxin that selectively inhibits serine/threonine phosphatases 1 and 2A. The decreased activity of protein phosphatase 2A (PP2A) has been observed in the pathology of AD and was proposed to be involved in hyperphosphorylation of tau. In line with the abovementioned molecular link to AD pathology, (ICV) OKA injection develops memory impairment in rats, making it suitable for further characterization as a potential AD model [24]. OKA-induced memory impairment is found to be associated with neuroinflammation. In OKA-injected rats, neuroinflammation was characterized by increased expression of proinflammatory cytokine TNF-α and IL-1β as well as total nitrite in both hippocampus and cortex [25].

Conclusion

Disease-specific animal models are indispensable for the understanding of possible disease mechanisms as well as for preclinical drug development. Undoubtedly, conventional transgenic models of AD are the basis of our today's in-depth understanding of several mechanisms that are probably involved in AD. However, since all potential Alzheimer's disease-modifying agents tested in these models have failed in phase-3 clinical trials, their application in drug discovery is under question.

Different strategies can be considered to bridge the gap between human AD pathology and rodent AD models. On one hand, major efforts should be undertaken to thoroughly characterize conventional animal models with newly available methods, to allow for more realistic translation of the results from animal models to human LOAD. On the other hand, etiology-based models should be established for LOAD. Thus far, several hypotheses regarding the probable etiology of AD have been suggested. However, appropriate in vivo models to test these hypotheses are still lacking. In this review, we synthesized the current information about rodent models potentially compatible with the inflammation hypothesis of AD.

All in all, the choice of an animal model should be an informed decision on behalf of the investigator. Nevertheless, using etiology-based models of LOAD may create a breakthrough in understanding of the disease pathology, designing precise diagnostic modalities and discovery of effective therapeutic agents.

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