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Review article

Reactive astrocytes in Alzheimer's disease: A double-edged sword

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ABSTRACT

Alzheimer's disease (AD) is a chronic and fatal disease, in which neuronal damage at its late stage cannot be easily reversed. Because AD progression is caused by multiple factors including diverse cellular processes, studies on AD pathogenesis at the molecular and cellular level are challenging. Based on the lessons from unsuccessful neuron-focused research for an AD cure, non-cell autonomous mechanisms including brain inflammation and reactive astrocytes have recently been in the spotlight as potential therapeutic targets for AD. Studies have shown that reactive astrocytes are not only the result of inflammatory defense reactions, but also an active catabolic decomposer that acts by taking up amyloid beta toxins. Here, we give an overview of the characteristics of reactive astrocytes as pathological features of AD. Reactive astrocytes exert biphasic effects, that is, beneficial or detrimental depending on multiple factors. Many efforts have been put forth for defining and characterizing molecular signatures for the beneficial and detrimental reactive astrocytes. In the foreseeable future, manipulating and targeting each established molecular signature should have profound therapeutic implications for the treatment of AD.

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1. Introduction

Alzheimer's disease (AD) is a devastating neurodegenerative disease that shows multimodal symptoms such as progressive cognitive impairment and changes in mood and behavior. AD comprises various stages of severity, such as pre-clinical AD, mild cognitive impairment (MCI), and AD dementia (Masters et al., 2015). The majority of AD cases (over 95%) appear in sporadic form, related to environmental factors or aging, whereas familial AD (less than 5% of cases) is caused by inherited mutations of AD-related genes such as amyloid precursor protein (APP) (Goate et al., 1991), presenilin 1 (PS1), or presenilin 2 (PS2) (Levy-Lahad et al., 1995; Sherrington et al., 1995). These genes are all related to the increase of amyloid beta production, which is one of the major features of

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AD. Because it is believed that the accumulation of amyloid beta aggregates triggers hyperphosphorylation of tau and causes neurodegeneration in AD, therapeutic strategies for AD are based on the "amyloid hypothesis," and the AD research field has undoubtedly put enormous efforts into regulating the level of amyloid beta over the last few decades. Nevertheless, the results remain largely ineffective. Anticipated phase III clinical trials of amyloid beta antibody (Solanezumab, funded by Eli Lily) and BACE inhibitor (Verubecestat, funded by Merck) were recently declared to have failed (Doody et al., 2014; Hawkes, 2017). Meanwhile, currently approved drugs for AD neurodegeneration targets have a very limited time window regarding their effect of slowing the disease progression, and these drugs are therefore not an effective treatment for the disease. These serial failures challenge the current amyloid hypothesis and the neurocentric view that many pharmaceutical companies have spent billions of dollars on, and necessitate a paradigm shift in the still obscure etiology of AD.

Neuronal death is a late-phase event in AD and represents a therapeutically irreversible state. However, reversibility is the key to find new strategies for an ultimate AD cure. Therefore, researchers have recently focused on the brain inflammation occurring before neurodegeneration in AD pathogenesis, and it is believed that targeting inflammatory mechanisms can reverse the process of disease progression. In this review, we will present an overview of the main characteristics of AD and the role of brain inflammation, especially the role of reactive astrocytes, on AD pathogenesis.

2. Features of AD

Patients with AD show toxic protein aggregates such as amyloid beta and tau tangles (Taylor et al., 2002). In 1906, Alois Alzheimer first observed amyloid plaque and neurofibrillary tangles (NFTs), which are histopathological hallmarks of AD, in the brains of patients with AD. Amyloid beta is normally produced and degraded in healthy individuals (Haass et al., 1993; Mawuenyega et al., 2010), although its role is not fully understood. It occurs in the form of monomers, oligomers, protofibrils, fibrils, and amyloid beta plaques. Among amyloid peptides of various lengths, the peptide of a length of 40–42 amino acids has aggregating properties, and the fibrillary form of amyloid beta is the principal component of amyloid plaques shown in extracellular space. When amyloid beta is progressively accumulated and levels are aberrantly elevated, the incidence rate of AD is significantly increased. It is in fact known that the amyloid beta clearance mechanism is disrupted in patients with AD (Mawuenyega et al., 2010), which means that maintaining appropriate levels of amyloid beta is important in physiological conditions. It has been reported that amyloid beta deposition starts decades before cognitive decline, and brain atrophy is detected by amyloid beta PET (position emission tomography) imaging (Villemagne et al., 2013). The Pittsburgh compound B (PiB), a radioactive carbon-11 analogue of the fluorescent amyloid due thioflavin-T62, binds to fibrillary amyloid beta and thus makes amyloid beta imaging possible *in vivo* (Cohen et al., 2012; Mathis et al., 2003). In contrast, NFTs accumulate in intraneuronal regions and are formed through hyper-phosphorylation of tau proteins. Tau tangles are correlated with disease severity (Augustinack et al., 2002; Bierer et al., 1995). Moreover, it is known that tau pathology itself can cause neurodegeneration(Ballatore et al., 2007).

Brain inflammation is ubiquitously observed in the AD brain, and mainly consists of glial activation, such as astrogliosis, and microglial activation (Serrano-Pozo et al., 2013; Itagaki et al., 1989). In his original descriptions, Alois Alzheimer firstly mentioned glial changes having fibers and large deposits in brain of patient with AD (Fig. 1C). He observed the morphological alterations of glial cells in the brain of his second patient, Johann F. Credit and drew the hypertrophied glial cells surrounding the plaque. (Fig. 1B). However, the precise role of those morphologically altered glial cells, which now we refer to reactive astrocytes, is largely unknown. In amyloid beta-overexpressing mice, an animal model of AD, reactive astrocytes and activated microglia appear surrounding amyloid plaques. As the number of plaques increases, gliosis becomes severe (Jo et al., 2014). It is known that the severity of gliosis is correlated with disease severity (Simpson et al., 2010). Despite its pervasive existence in the AD brain, gliosis has long been considered an epiphenomenon following neurodegeneration. However, since temporal correlation studies showed that inflammatory changes precede the clinical symptoms of AD and amyloid beta deposition (Tarkowski et al., 2003), research has increasingly been focused on the importance of immune states in AD pathogenesis. However, the contribution of glial cells such as astrocytes and microglia on AD pathogenesis is largely unknown.

Neurodegeneration is a final cellular symptom of AD. Neuronal death takes place in brains of patients with AD. The proposed mechanisms of neurodegeneration include excitotoxicity via glutamate, nitrosative stress, tauopathy, and axonal degeneration leading to programmed cell death (PCD) (Cusack et al., 2013) and/or autophagic cell death (ACD) (Nixon, 2013). When the extracellular glutamate concentration is increased above physiological levels, NMDA-mediated excitotoxicity leads to the death of neurons (Hynd et al., 2004; Coyle et al., 1981). Nitrosative stress is caused by excess production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which lead to cell death by nitration of proteins (Nakamura and Lipton, 2007; Lipton et al., 1993). Tauopathy consists of neurofibrillary tangles that are made from hyperphosphorylated tau protein aggregation and directly kill the cell (Spillantini and Goedert, 2013; Yoshiyama et al., 2007). Tau hyperphosphorylation is mediated by the GSK3 beta pathway, which is activated by oxidative stress (Zhang et al., 2005). However, the etiology of neurodegeneration is not clear. In AD, brain atrophy is also shown on MR images of human patients (Zhang et al., 2011). The degree of brain atrophy correlates with the neurofibrillary tangle pathology defined by Braak stage, while it is not correlated with the amyloid beta deposition (Braak and Braak, 1991; Whitwell et al., 2008; Josephs et al., 2008).

To attenuate the disease progression, several drugs are being used such as acetylcholinesterase inhibitors (Rivastigmine, Galantamine, Donepezil) and N-methyl D-aspartate receptor antagonist (Memantine). Rivastigmine, Galantamine, and Donepezil are administered to patients with mild to moderate AD (Cruz Jentoft and Hernandez, 2014; Hirsch, 2006; Greenberg, 2000), whereas Memantine is prescribed to patients with moderate to severe AD (Finucane, 2004). However, these drugs cannot reverse the disease progression and have many adverse side effects (Liu et al., 2002; Inglis, 2002). These shortfalls of the currently available AD drugs probably come from the fact that we still do not have a complete and detailed picture of the sequence of events during the progression of AD. There is thus an urgent need for finding therapeutic targets according to the time-ordered sequence of events during disease progression and for developing new drugs for AD.

3. Brain inflammation in AD pathogenesis

It is generally considered that identification of the time-ordered sequence of pathogenic events is crucial for elucidating the causal relationship between known biomarkers and AD (Jack et al., 2010). The temporal order of AD biomarkers in disease progression needs thus to be addressed. Research shows that inflammatory signals in the brain, including glial activation, are detected early during the pre-symptomic phase of AD progression with amyloid beta production (Jack et al., 2010). Recently, NSAIDs (non-steroidal

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