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Review

Infection, systemic inflammation, and Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a leading cause of dementia among elderly. Yet, its etiology remains largely unclear. In this review, we summarize studies that associate systemic infection and neuroinflammation with AD, while highlighting that early-life or life-long exposure to infectious agents predisposes one to develop AD at a later age.

Keywords: Alzheimer's disease; Infection; Inflammation; Sporadic; Risk factors; Environment

1. Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by the decline of cognitive functions, particularly learning and memory. Currently, over 5 million people are suffering from AD in the U.S. alone, and trajectory of the number of patients in 2050 is expected to reach to as many as 16 million. AD is the most common form of dementia, and patients have an average life expectancy of 5–9 years after diagnosis. To date, no effective, mechanism-based treatment strategy is available to halt the progression of the disease. This is largely because the etiopathogenesis of AD remains one of the major unsolved mysteries in the field of neuroscience [1,2].

The mainstream of current FDA-approved pharmacological treatment for AD is to ameliorate cognitive decline by restoring neurotransmitter signaling between neurons. A large body of research carried out from the late 60's to the mid 80's placed neurotransmitters dysregulation, specifically acetylcholine, as the major contributor to the deterioration of the mental abilities observed in AD [3]. In fact, four of the five medications approved by the FDA for prescription to AD patients are aimed to increase extracellular levels of acetylcholine by delaying its degradation (the acetylcholinesterase inhibitors: tacrine, rivastigmine, galantamine and donepezil). The fifth approved drug is memantine, a partial antagonist for the ionotropic glutamate NMDA receptor [4]. Memantine presumably reduces calcium-mediated glutamate excitotoxicity, hence slowing synaptic and neuronal loss characteristically observed in the AD brain [5]. Although these treatments have proven to maintain cognitive function in AD patients, the therapeutic effect is transient and primarily symptomatic. These treatments are not mechanism-based and do not seem to have any disease-modifying effects, either. Moreover, no significant proof supports that these drugs play a role in the prevention of cognitive decline or the reversal of pathological hallmarks and neurodegeneration in AD [2].

2. Pathological hallmarks

The AD brain displays two pathological characteristics that up-to-date are required postmortem observations for confirming a diagnosis of AD: extracellular insoluble senile plaques composed of amyloid-beta (Aβ) fibers, and intraneuronal neurofibrillary tangles (NTFs) which main component is hyperphosphorylated and aggregated tau protein [2]. An increase in the ratio of fibrillogenic Aβ42 is observed in a vast majority of genetic mutations that cause familial AD (FAD)

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[6]. Recently, it was discovered that soluble Aβ oligomers (2–6 peptides) and even intracellular Aβ42 that are present within neurons in early stages of the disease exhibit far more toxic effects than plaques [7]. FAD is produced by mutations on the genes encoding for the amyloid precursor protein (APP), presenilin 1 or presenilin 2 proteins. These mutations have been used for the generation of most AD mouse models, which are one of the core tools employed for the study of the disease [8].

Aβ is produced by the non-prevailing proteolysis of APP. In the Aβ-producing pathway, APP is proteolytically cleaved by the beta-site APP-cleaving enzyme 1, an aspartyl protease that cleaves at position 99 from the C terminus. Subsequently, the C99-fragment is further cut by the gamma secretase resulting in Aβ generation. Gamma secretase is a complex of proteins composed of nicastrin, anterior pharynx defective 1 (APH1), presenilin enhancer 2 (PEN2), along with its catalytic domain presenilin 1 or presenilin 2. On the contrary, in the prevailing pathway, proteolysis of APP is produced by one of the alpha-secretases (ADAM9, ADAM10, ADAM17) that cuts within the Aβ precursor region, thereby avoiding formation of Aβ [7].

NTFs, the other signature pathological hallmark of AD, are tau-positive intracellular inclusions found in pyramidal neurons. Under physiological conditions, tau is a highly soluble protein involved in microtubules stability and axonal transport [9]. Hyperphosphorylated tau is insoluble and prone to form filaments with no affinity for microtubules [10]. Therefore, the mechanisms that regulate tau phosphorylation are matter of extensive study [11].

It is important to note that other fundamental brain pathological features of AD include neuronal loss, synaptic degeneration and activated inflammatory cells in the brain [2]. Synaptic proteins have been reported to be dramatically reduced in AD patients, and in some advanced cases, major brain atrophy is observed [12]. Synaptic loss is closely correlated with cognitive decline in AD, making it clear the vital role that this feature plays in the disease [13]. Another critical component of AD pathology is inflammation. Reactive microglia and astrocytes adjacent to Aβ plaques is a common observation in the AD brain [14]. It is thought that activated glia is at first beneficial for degrading Aβ plaques [15]. However, chronic inflammation leads to the production of several cytokines that have been demonstrated to exacerbate other AD pathologies [16].

3. Hypothesized molecular mechanisms of AD

Decades of research and findings had neuroscientists proposing three major hypotheses on the etiopathogenesis of AD. In chronological order, the “cholinergic hypothesis of AD” was first proposed due to reduced levels of several key proteins involved in the production, reuptake and release of acetylcholine reported in AD patients [17]. To date, this hypothesis still heavily influenced the current pharmacological management of AD as described earlier.

In 1991, John Hardy and David Allsop proposed the “amyloid cascade hypothesis” owing to accumulating evidence that Aβ is the primary initiator of AD pathogenesis. The hypothesis posits aberrant accumulation of Aβ species upstream of NTFs formation, which are then followed by synaptic disruption, neurodegeneration and cognitive decline [18]. This hypothesis is well supported by the fact that all FAD mutations lead to accelerated Aβ deposition in the brain by increasing the production of total Aβ species or highly toxic Aβ42, or by enhancing its aggregation properties. The hypothesis may also be well extended to non-FAD sporadic cases as certain non-genetic risk factors for AD, such as strokes and traumatic brain injuries, have been shown to upregulate APP expression and subsequent production of Aβ species [19,20]. In general, abnormal Aβ deposition starts decades before developing any clinical signs of cognitive decline [21], and its accumulation may be influenced by insults that initiate the overproduction of APP and/or by the life-long capacity of Aβ clearance [22]. Once buildup, these neurotoxic peptides play key roles in dysregulating the inflammatory response in the brain that, in turn, exacerbates the neuropathology of AD [23–25].

More recently, the significance of systemic inflammation in the etiology of AD has gotten so prevailed that Krstic and Knuesel coined the term “inflammation hypothesis of AD” in their review that seem more relevant to the development of the sporadic form of the disease than the familial form [26]. Briefly, they hypothesize that chronic inflammation dysregulates mechanism for clearing misfolded or damaged neuronal proteins in aging brains that lead to tau-associated impairments of axonal integrity and transport, accumulation of APP, formation of paired helical filaments, and synaptic dysfunction. Concomitantly, chronic inflammation also primes microglia to a hyper-reactive state that impairs in dystrophic neurites clearance, which in turn, generates a neurotoxic pro-inflammatory environment that affects neighboring neurons. Persistent neuroinflammation follows and formation of senile Aβ plaques and NFTs amplifies, leading to prominent neurodegeneration and resultant cognitive decline.

4. Risk factors

Despite the major role that FAD has played in our understanding of the disease, FAD only accounts for 5% of the total number of patients, with sporadic cases being the vast majority for which the underlying etiology is unknown. Yet, numerous genetic and environmental risk factors have been identified and extensively studied [2]. Among them, aging is considered the most important risk factor for AD. In the U.S., population between the age of 60 and 64 has an AD incidence of below 1%. However, this frequency doubles every 5 years on individuals over 65 years old, and by the age of 85, nearly half of this population is at high risk, and one third of them would be diagnosed with AD [27].

Genetic risk factors, or susceptible genes, are being investigated in AD patients and have shown strong cause–effect relationships. For example, aside from being responsible for genetic mutations in FAD, a gene encoding apolipoprotein E has been identified as the most influential gene to modulate the risk for developing AD at later ages [28]. One copy of ε4 allele