·Editorial·

Alzheimer's disease: from molecule to clinic

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Alzheimer's disease (AD) is the most common neurodegenerative disorder and is characterized pathologically by the progressive intracellular accumulation of neurofibrillary tangles and extracellular deposition of plaques in the brain. Since hyperphosphorylated tau and β-amyloid (Aβ) are respectively the major components of the tangles and the plaques, recent studies have mainly focused on the alterations associated with these two molecules. Clinically, AD features memory deterioration. More than 6 million patients in China alone are suffering from this devastating disease, and this figure is increasing with the acceleration of population ageing. Although many specific aspects of AD have been documented, the disease is hard to diagnose in the early stage and the efficacy of current treatments is very limited. Therefore, AD is attracting worldwide attention.

To help scientists and clinicians in the field better understand AD, we have organized this special issue. The 18 papers include 3 original research articles and 15 reviews invited from 17 laboratories in China, the United States, Canada, and Sweden. The content of this special issue covers the most recent progress in understanding the epidemiology, molecular pathogenesis, and potential diagnostic and therapeutic strategies of AD.

AD is a multi-factorial disorder and the etiological factors are not fully understood. Over 95% of cases are sporadic in nature with onset in people over 65 years old, suggesting that aging is an independent risk factor for AD. To explore how aging is involved in AD neuronal loss, He's group demonstrates that uric formaldehyde is negatively correlated with cognitive abilities in older adults, and the increased formaldehyde also occurs in aged cell cultures. Furthermore, treatment of cells with certain concentrations of formaldehyde reduces cell viability and damages cell morphology[1]. Several microRNAs are implicated in aging. Zhang's group shows that miR-206 is upregulated in the hippocampus, cerebrospinal fluid, and plasma of APP/PS1 transgenic mice, and this downregulates the expression of brain-derived neurotrophic factor[2]. By intracellular injection of $A\beta_{42}$ in *Drosophila*, Huang's group reveals that the intraneuronal accumulation of $A\beta_{42}$ induces an age-dependent slowdown of neuronal transmission with a reduced transmission velocity of neuronal signals in the giant fiber system[3]. These new findings suggest that improving brain metabolism by targeting specific microRNAs, formaldehyde, and $A\beta_{42}$ during aging may be tractable strategies to protect neurons from degeneration.

Since there is, as yet, no efficient way to repair degenerating neurons, early diagnosis is critical for preventing or delaying neurodegeneration in AD. To achieve early diagnosis, longitudinal population-based studies on the application of non-invasive techniques and biomarkers are indispensable. Pei and Wang have analyzed 25 published studies of elderly Chinese residents from Mainland China, Hong Kong, Taiwan, and Singapore. The results show that the prevalence, incidence, and risk factors for dementia in Chinese populations are comparable to those in other ethnic groups, but no conclusive results were found for the prognosis of dementia[4]. Application of multi-modal imaging has recently shown great potential for the non-invasive clinical screening and diagnosis of AD. Han introduces each of the magnetic resonance imaging modalities used in longitudinal studies of AD and discusses the future direction for these types of study[5]. By focusing specifically on changes in the topological organization of large-scale structural and functional brain networks, He

proposes that AD is associated with disrupted segregation and integration in the networks, and brain connectomics studies may uncover imaging markers for clinical diagnosis and for evaluating treatment of AD[6]. As for cerebrospinal fluid biomarkers, Yang summarizes the novel candidates identified by highly-sensitive and high-throughput proteomic techniques in addition to the previously recognized Aβ and tau proteins. They also provide perspectives on how biomarker discovery for AD is evolving[7].

Deregulation of brain metabolism plays an important role in the initiation and progression of AD. For instance, reduction of insulin, insulin receptor binding, or downstream signaling responsiveness has been reported in the AD brain. Gong reviews the important role of brain insulin deficits in the development of sporadic AD, and promising therapeutic implications by targeting the brain insulin pathway for the treatment of AD and other neurodegenerative disorders[8]. Abundant studies show that oxidative stress is an essential process in AD pathogenesis, promoting Aβ deposition, tau hyperphosphorylation, and the subsequent loss of synapses and neurons. Zhu and Zhong analyze how oxidative stress or its synergistic effects along with other environmental and metabolic factors may affect neuronal functions and cause neuronal failure[9-11]. Cholinergic hypofunction is an early pathological feature of AD. Zhang reviews recent progress in understanding the functional involvement of the M1 muscarinic acetylcholine receptor in AD and in developing specific agonists for AD treatment[12]. Although deficient autophagy has been reported in AD, stimulation of autophagy is not always beneficial. By summarizing the recent publications on autophagy in AD, Jia emphasizes that, during the implementation of autophagy modulation therapies, the nature of the autophagic defect, the timing of intervention, and the optimal level and duration of modulation should be considered[13]. Recent genome-wide association studies demonstrate that neuroinflammation and lipid deregulation play crucial roles in AD. Zhang reviews the literature on the roles, mechanisms, and interrelations of neuroinflammation with Aβ and apolipoprotein E alleles[14]. Liu summarizes the involvement of different lipids in AD[15].

The tau abnormality alone can cause neurode-generation and cognitive impairments that have been detected in over twenty neurodegenerative disorders, thus it has attracted widespread interest as a target protein. Alonso discusses the biological functions of tau in microtubule assembly and stabilization and its interaction with other proteins. She also analyzes how different post-translational modifications of tau change its biological functions and the possible approaches to target these alterations[16]. The adult human brain expresses six isoforms of tau by alternative splicing of its pre-mRNA at exons 2, 3, and 10. Liu demonstrates that abnormal regulation of tau exon 10 splicing causes neurodegeneration, and reviews the regulation of this splicing by *cis*-elements and *trans*-factors[17]. It is widely believed that tau hyperphosphorylation causes neurodegeneration, however it is not clear how. Based on the new finding that tau regulates cell viability, Wang proposes that the nature of AD neurodegeneration is the consequence of aborted apoptosis induced by tau hyperphosphorylation, therefore, proper manipulation of tau phosphorylation could be promising in arresting AD neurodegeneration[18].

Taken together, the papers presented in this special issue cover the wide spectrum of AD. We hope that this will promote new studies that provide a better understanding of this disease, and more importantly, in developing novel molecular and cellular approaches to effectively prevent it or at least delay its progression.

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