Recent progress in neurodegenerative disorder research in China

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Neurodegenerative disorders, including Alzheimer’s disease (AD) and Parkinson’s disease (PD), are common disorders of the central nervous system among aging populations. In the last 10 years insights concerning the etiology, diagnosis and pathogenesis of these diseases have come from research carried out by Chinese neuroscientists. Their findings include the description of Chinese patients with autosomal recessive early-onset PD, the function of the tau protein, molecular mechanisms underlying protein aggregation, and the identification of biomarkers for AD diagnosis and molecules/compounds with potential neuroprotective activities.

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Neurodegenerative disorders are a group of diseases characterized by progressive neuronal loss in the CNS. Neurodegenerative disorders usually include but are not limited to Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington’s disease (HD) and amyotrophic lateral sclerosis (ALS). Among them, AD and PD are the most prevalent. For example, the prevalence of PD in the US is ~ 1% at 55 years of age. Over one million Americans suffer from PD and some 50000 Americans each year are diagnosed with PD. The prevalence of PD in China, particularly in Chinese cities, is very close to that in the U.S. According to the survey conducted by the Xuanwu Hospital of the Capital Medical University in 2000, the prevalence of PD in the Beijing area is 1.17% at 55 years of age [1]. The prevalence of AD is greater – ~5% at 65 years of age in China. The number of people affected by AD and PD is likely to increase in the coming decade due to the expansion of the aged population.

Neurodegenerative disorders are a burden to society in terms of lost productivity and health-care costs. Chen and his colleagues [2] at Ruijin Hospital in Shanghai have assessed the annual direct and indirect costs of each AD patient in Shanghai area to be RMB 19001 yuan (USD 2384) per year. The total cost was significantly associated with the degree of severity. The highest health care cost of AD in their study was the cost of medication, accounting for 62% of the direct health care cost – about twice that in the U.S. but close to that found in Turkey and Argentina. These statistics indicate that China faces comparable public health issues to other leading nations. This review will report and discuss the research progress on neurodegenerative disease achieved in the last several years in China. AD and PD are the major focus of this review.

1 Etiology of AD and PD

1.1 Genetic mutations

The etiology of PD remains unclear. Linkage analysis in large families and the positional cloning of an increasing number of genes that cause monogenic forms of PD have provided insights into the pathogenesis of this disorder. Four genes, Parkin, PINK1, DJ-1 and ATP13A2 are among the 13
loci which have been identified as being responsible for autosomal recessive early-onset Parkinsonism (AREP). Tang [3] at Xiangya Hospital in Changsha performed mutation analysis of these 4 genes in Chinese PD patients with AREP. They studied the prevalence of mutations in these 4 genes in 29 Chinese unrelated families with AREP, using direct sequencing analysis and real-time quantitative PCR analysis assay. There were 14 families (48.3%) with mutations of the Parkin gene, 2 families (6.9%) with mutations of the PINK1 gene, and 1 family (3.4%) with a mutation of the DJ-1 gene. No pathogenic mutations in the ATP13A2 gene were found in these families. Three novel Parkin gene mutations (c.G859T, c.1069-1074delGTGTCC, and c.T1422C) and one novel DJ-1 gene mutation (c.T29C) in these patients were found. This data suggests that the Parkin gene mutation is the most common pathogenic factor in Chinese patients with AREP [3]. This is the first genetic characterization of Chinese PD patients with AREP.

Patients with familial neurodegenerative disorders are likely to harbor heterozygous mutations in more than one AREP-linked gene. Tang’s group [3] identified a Chinese family with PD harboring novel heterozygous missense mutations in both the PINK1 and DJ-1 genes respectively encoding DJ-1A39S and PINK1P399L. Coexpression of the mutated forms of these two proteins in SH-SY5Y neuroblastoma cells significantly potentiated their susceptibility to MPP⁺-induced cell death. This study reports the first case of autosomal recessive PD with digenic inheritance and demonstrates that DJ-1 and PINK1 physically associate and collaborate to protect cells against stress via a complex formation.

However, not all gene mutations are deleterious to neuronal cells. By systematic screening of the gene promoter region of ADAM9 (a disintegrin and metalloproteinase), Jia’s group [4] at Xuanwu Hospital in Beijing found 4 polymorphisms: −542C/T (rs10105311), −600A/C (rs7840270), −963A/G (rs6991968) and −1314T/C (rs7006414) in Chinese AD patients. It is known that progressive neurodegeneration in AD is associated with the formation of amyloid β-peptides (Aβ peptides) and their deposition in the brain, and ADAM 9 cleaves the amyloid precursor protein (APP) within the Aβ domain and prevents the generation of Aβ peptides. Some of these polymorphisms identified appeared to increase ADAM9 transcriptional activity, suggesting that ADAM9 promoter polymorphisms may be protective against sporadic AD [4].

In addition, hereditary spastic paraplegia is a group of inherited neurodegenerative disorders with the shared characteristics of slowly progressive spasticity and weakness of the lower limbs. A novel candidate locus on chromosome 11p14.1–p11.2 for autosomal dominant hereditary spastic paraplegia has been identified by the laboratory of Tang BeiSha [5] in Changsha.

2 Molecular mechanisms underlying pathological changes in AD and PD

2.1 Function of the tau protein

One of the most prominent pathological features of AD is the hyperphosphorylation of the tau protein, which forms neurofibrillary tangles. Tau is a major neuronal microtubule-associated protein, and is crucial for microtubule assembly and stabilization. There is growing evidence showing that the tau protein interacts with DNA and serves as a multifunctional protein. It has recently been found in the nucleus and is associated with DNA, but the biological role of nuclear tau remains obscure.

He’s laboratory [9] at the Institute of Biophysics of Chinese Academy of Sciences (CAS) in Beijing has found that human tau protein represses DNA replication in vitro. By using atomic force microscopy, they found that tau as a monomer binds to DNA to form “beads-on-a-string” complexes at a molar ratio [tau]/[DNA] of 1:10. They went a step further by showing that tau binding on DNA inhibited DNA replication, but did not affect RNA transcription in vitro [10].

Although it is currently not known whether or not this newly revealed function of the tau protein has any significant implication for AD pathogenesis, there is evidence suggesting that the tau protein is a factor under pathological conditions, such as stress. It was found that tau protected DNA from thermal denaturation, and improved the renaturation of DNA. Circular dichroic spectra results showed that addition of tau prevents conformational changes in a DNA double helix in stress. Furthermore, tau protected DNA from hydroxyl radical (•OH) attack in vitro, implying that tau functions as a DNA-protecting molecule against free radicals [11].

One may further speculate that altered phosphorylation of the tau protein may reduce its capability of DNA protection during oxidative stress, in addition to the impairment of microtubule assembly and stabilization.

2.2 Protein aggregation

It has become clear that many neurodegenerative diseases