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EDITORIAL

Special issue on neurodegenerative diseases and their therapeutic approaches

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Aging is the strongest risk factor for most neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis. As the aging population is increasing, these neurodegenerative disorders are becoming major social issues in many countries. Interestingly, these diseases share a common pathological phenotype; the accumulation of misfolded and aggregated proteins in the brain. Mounting evidence suggests that there are mechanistic links between toxic protein aggregation and neurodegenerative diseases. With a better understanding of the pathogenesis of these disorders, discovery efforts for disease-modifying therapeutics have markedly increased in recent years. This special issue, titled 'Neurodegenerative diseases and their therapeutic approaches', discusses the underlying pathogenic mechanisms and therapeutic implications for AD and other age-associated neurodegenerative disorders.

Aaron Ciechanover and Yong Tae Kwon provide a comprehensive overview of the proteolytic pathways in neurons, with a special emphasis on the ubiquitin–proteasome system (UPS), chaperone-mediated autophagy and macro-autophagy. They also discuss the role of protein quality control in the degradation of pathogenic proteins involved in several neurodegenerative diseases. The initial discovery of the UPS was published by Dr Aaron Ciechanover, who won a Nobel Prize in 2004[1] (http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2004/ciechanover-lecture.pdf).

Among the age-associated neurodegenerative diseases, AD is the most common neurodegenerative disease. Its symptoms include cognitive impairment, disturbance of the sleep–wake cycle and circadian rhythms, and dysfunctions of metabolism, such as insulin-resistance and mitochondrial dysfunction. The pathological hallmarks of AD are intracellular neurofibrillary tangles, extracellular senile plaques and neuronal cell loss. Neurofibrillary tangles are mainly composed of hyperphosphorylated tau, and the major component of senile plaques is amyloid-β (Aβ) peptides. Many lines of evidence have shown the strong association between the two aggregated molecules, Aβ and tau, and AD pathogenesis.

Holtzman's group reviews multiple molecular mechanisms by which sleep disturbance and disruption of circadian rhythms may affect AD pathogenesis. In addition, they discuss potential therapeutic strategies for AD by targeting the circadian clock and sleep–wake system.

Bhumsoo Kim and Eva L Feldman focus on the dysfunction of insulin signaling in AD pathogenesis. Insulin signaling has diverse roles in the brain, such as cognition, memory, synaptic plasticity and neurogenesis. As AD patients show the disrupted glucose metabolism in the brain, it is reasonable to link insulin resistance and AD pathogenesis. The authors also suggest that several diabetes therapies targeting insulin signaling may have potential therapeutic benefits in AD patients.

Mook-Jung's gourp review the mitochondrial dysfunction in several neurodegenerative diseases, including AD. Reactive oxygen species (ROS) is a well-known stress factor for the central nervous system. ROS induces mutations in mitochondrial genes, leading to more ROS generation by exacerbating mitochondrial dysfunction. This vicious cycle between ROS and mitochondrial dysfunction further stresses neurons, eventually leading to cell death. Antioxidant therapy restoring mitochondrial function might be one of potential therapeutic strategies to treat AD and other neurodegenerative disorders.

Proper maintenance of neuronal circuits is critical for learning and memory. The loss of neurons and neuronal processes directly contributes to cognitive declines in AD. Because many clinical trials with small molecule approaches, as well as anti-Aβ immunotherapy has failed, cell replacement therapy using human embryonic stem cell- or induced pluripotent stem cell -derived neural cells is gaining attention as a potential treatment for AD. Huang's group reviews the current status and future prospects of stem cell therapy for AD and other related disorders.

Because AD and other age-associated neurodegenerative disorders are chronic diseases, many factors might be involved in the onset and progression of these diseases. The five articles in this special issue provide comprehensive reviews of the multiple pathogenic mechanisms underlying AD and related

neurodegenerative disorders. In addition, each review suggests potential therapeutic targets for the treatment of AD. Taken together, this special issue, titled 'Neurodegenerative diseases and their therapeutic approaches', in *EMM* is an invaluable resource for understanding the current status and future perspectives of AD and related neurodegenerative disorders.

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