ISSN 0006-2979, Biochemistry (Moscow), 2018, Vol. 83, No. 9, pp. 1007-1008. © Pleiades Publishing, Ltd., 2018.
Published in Russian in Biokhimiya, 2018, Vol. 83, No. 9, pp. 1269-1271.

Different Pathways to Neurodegeneration

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Received June 25, 2018

Abstract—The current issue is dedicated to the studies of neurodegenerative diseases and memory. Molecular mechanisms and mutant genes have already been revealed for many neurodegenerative diseases. However, in many cases the cause of selective death of neurons in different brain regions remains unclear. Genetic predisposition and aging are well established risk factors in many neurodegenerative diseases. A large body of evidence has been obtained that shows an important role of immune factors in the modulation of neurodegenerative processes. The progress in the treatment of neurodegenerative diseases requires new cell models for identification of non-canonical pharmacological targets and development of approaches for memory regulation. Gene therapy technologies based on genome editing and RNA interference methods are among promising approaches for repairing primary molecular defects underlying neurodegenerative pathologies.

DOI: 10.1134/S0006297918090018

Keywords: neurodegeneration, mutant genes, aging, memory, Alzheimer's disease

This journal issue is dedicated to the problems of neurodegeneration and memory.

Humans suffer from a broad range of neurodegenerative diseases, whose clinical picture is strongly determined by the topography of massive neuronal damage in the brain. Parkinson's disease is accompanied by the death of dopaminergic neurons in the basal ganglia that control body movements. Basal ganglia damage is observed in the Huntington's chorea resulting in uncontrolled random movements. Accumulation of extracellular amyloid plaques and intracellular neurofibrillary tangles in Alzheimer's disease causes neuronal death in the hippocampus and temporal lobes of the neocortex responsible for the memory formation. As a result, affected individuals lose memory, especially of the recent events. Degeneration gradually spreads to the adjacent brain regions and is often accompanied by behavioral changes. Reviews and experimental articles in this journal issue are focused on the molecular and cellular mechanisms of these impairments (and not on neurodegenerative disorders related to traumas or vascular impairments, e.g., stroke). Some articles discuss the mechanisms of memory regulation, which is important in regard to the development of new approaches for the treatment of memory deficiencies observed in various types of dementia.

Adult human brain contains up to 70-100 billion neurons and a huge number of synaptic connections between them. That makes brain the most complex biological system in nature. Neurons have the longest life span among all organism's cells. Most of our neurons already exist in the brain by the time of birth and survive for over 100 years in centenarians! Normally, the loss of neurons in a course of aging is slow. However, massive death of neurons may occur in specific brain regions leading to various neurodegenerative pathologies that affecting humans in mid- to late life.

What makes adult neurons vulnerable to death signals? What are universal and specific mechanisms that underlie neurodegenerative disorders? Aging and genetics are the most significant risk factors in neurodegeneration. Genetic studies clearly show that defects in many unrelated genes and molecular pathways lead to neuronal death and, as a result, sensory, motor, and cognitive impairments, memory loss, and nervous system disorders, such as macular degeneration, Alzheimer's and Parkinson's diseases, amyotrophic lateral sclerosis, Huntington disease, and others. Mutations in certain genes were found to be associated with familial forms of neurodegenerative diseases. In some cases, gene mutations are highly penetrant and causative, e.g., the tri-

nucleotide repeat expansion in a single gene in the Huntington disease or the missense mutations in presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), and amyloid precursor protein (*APP*) genes in Alzheimer's disease. The less penetrant gene variations may also contribute as risk factors to common forms of neurodegeneration, e.g., Parkinson's and late-onset Alzheimer's diseases.

Aggregation of unfolded proteins (e.g., formation of amyloid plaques) in specific brain areas is a common feature of neurodegenerative disorders. However, accumulation of these insoluble proteins in brain may be insufficient for the degenerative process *per se*. For example, some elderly individuals were found to have a large number of amyloid plaques without exhibiting any signs of neurodegeneration. It is possible that brain neurons of these subjects are less sensitive to death signals triggered by plaque accumulation in the brain.

Neurons are not alone in the brain. Brain contains various non-neuronal cells, mainly glia, that outnumber neurons in certain brain regions. For example, the ratio between glial and neuronal cells in the human frontal cortex is ~2 : 1, which is higher than in other anthropoid primates, such as New and Old World monkeys and apes.

Enlargement of human brain in evolution has come with a high metabolic cost [1]. Human brain comprises only ~2% body mass but utilizes >20% total glucose of the body. It is possible that relative increase in the number of glial cells in human brain reflects the metabolic demands of neurons in expanded brain. Changes in mitochondria-dependent metabolism may contribute to the neuronal death or survival. The regulation of brain metabolism is of great interest in searching for the factors modulating neurodegeneration.

The population of glial cell includes astrocytes, oligodendrocytes, Schwann cells, satellite glial cells, and microglia. There is growing body of evidence that non-neuronal cells, in particular, microglia (brain immune cells), play a significant role in neuroinflammation and neurodegeneration. Numerous data show that impairments in innate immunity contribute to the encephalopathy by triggering inflammation in various neurodegenerative diseases. The role of adaptive immune system in neuronal death in brain is yet poorly studied. Comprehensive genome-wide association study (GWAS) for 25 brain disorders has been recently performed that included 265,218 patients and 784,643 control subjects [2]. This study revealed shared genetic risk factors for psychiatric diseases (e.g., depression and schizophrenia), but found no overlap between genetic factors for neurological and psychiatric diseases or for different neurological diseases. In this regard, we should mention interesting genetic data for the HLA (or MHC, major histocompatibility complex) locus. The HLA (human leukocyte antigen) locus is the most consistently reported genomic region genetically associated with schizophrenia. Association of the HLA locus with clinically unrelated types of dementia and other neurodegenerative diseases has also been shown (see in this issue).

The role of brain immune system and peripheral immune system is a new and exciting area of neurodegeneration studies. We can already suggest that the clinical properties of neurodegenerative pathologies are defined by genetic variations in specific genes and brain regions primarily affected by massive death of neurons. Other factors, such as individual brain capacity (e.g., memory) and immune system response, may also modulate neurodegenerative processes.

This special journal issue includes reviews of genetic, cellular, and immune aspects of common neurodegenerative pathologies, from Huntington chorea to Parkinson's and Alzheimer's diseases. Given that no efficient therapy has been yet found for neurodegenerative diseases, development of new models of neurodegenerative disorders (e.g., human iPSCs) and searching for non-canonical pharmacological targets are essential for further progress in the field. Since many neurodegenerative disorders (genetic forms of Parkinson's disease, amyotrophic lateral sclerosis, and Alzheimer's disease) are determined by mutations in already known genes, development of gene therapy methods using genome editing and RNA interference remains a promising approach for repairing molecular defects resulting in neurodegenerative diseases.

Funding

The work was supported by the Russian Science Foundation (project 14-44-00077) and National Institutes of Health (project R01AG054712).

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