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Proteinopathies

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Annotation: This article provides information about proteinopathies - a group of diseases that result from the accumulation of misfolded or aggregated proteins in cells. The molecular mechanisms, main causes and pathological consequences of proteinopathies are reviewed. The most important proteinopathies, such as Alzheimer's, Parkinson's, amyloidosis and prion diseases, are also described, and their clinical features, diagnostics and potential treatment methods are analyzed. This article helps to form fundamental concepts of proteinopathies and study current research directions.

Keywords: proteinopathy, misfolded proteins, neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, amyloidosis, prion diseases, protein aggregation, cell pathology, molecular mechanisms.

Introduction: Proteinopathies are a group of diseases that occur as a result of the accumulation of misfolded or misdistributed proteins in cells. This process disrupts the normal function of cells and leads to the development of various degenerative and chronic diseases. Proteinopathies include serious pathologies such as Alzheimer's, Parkinson's, Huntington's diseases, amyloidosis and prion diseases, which mainly affect the nervous system and other vital organs. The causes of

the development of these diseases are associated with the incorrect conformation of proteins, impaired degradation processes and insufficient functioning of cellular defense systems. As a result, proteins accumulated in the form of amyloid fibrils or toxic oligomers cause cell death. This article reviews the mechanisms of development, main causes, clinical symptoms and modern treatment methods of proteinopathies.

Methodology

Proteinopathies are a class of diseases characterized by the accumulation of misfolded or misshaped proteins in cells. These proteins often become toxic, impairing cellular function and can lead to cell death. Protein deposits disrupt the structure and function of cells, causing severe damage, especially in sensitive systems such as the nervous system [1]. Proteinopathies are associated with the most common neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis (ALS), Frontotemporal dementia (FTD), and the recently identified LATE syndrome. Amyloid-beta and tau proteins play a key role in Alzheimer's disease, and these proteins accumulate between and within neurons in the brain. Amyloid-beta plaques disrupt signal transmission between neurons, while tau protein disrupts the microtubule system inside neurons, which limits the movement of nutrients along the neurons.

Results and Discussion

As a result of the accumulation of these two proteins, neurons die and memory, thinking, behavior and other cognitive functions are impaired [2]. In Parkinson's disease, a protein called alpha-synuclein misfolds and forms Lewy bodies. They affect dopamine-producing neurons in the nigrostriatal pathway, which disrupts the movement control system. Parkinson's disease is characterized by tremors, slow movement, muscle stiffness and loss of balance. In this disease, Lewy bodies, which are formed as a result of misfolding of the protein, can later lead to cognitive impairment, that is, dementia. In ALS, a protein called TDP-43 misfolds inside motor neurons, disrupting their function. This protein leaves its place in the cell nucleus and aggregates in the cytoplasm. These aggregations disrupt the functioning of neurons, leading to their degeneration [3]. Patients gradually lose movement, muscles become weak, and it becomes difficult to speak, swallow, and breathe. This disease progresses very quickly, and there is currently no effective way to stop it. Frontotemporal dementia is also associated with the incorrect assembly of TDP-43 or tau proteins. This disease affects the frontal and temporal parts of the brain, which leads to changes in personality, behavior, and language. FTD mainly occurs in middle-aged people, and patients lose control of their behavior. It is manifested by a decrease in vocabulary, difficulty communicating, emotional apathy, and abnormal social behavior [4]. The recently identified LATE (limbic-predominant age-related TDP-43 encephalopathy) is particularly common in older people and presents with symptoms similar to Alzheimer's disease. In this case, the TDP-43 protein also misfolds and accumulates in the limbic system. It is argued that LATE may be an important cause of dementia, which affects a large part of the elderly population. Another characteristic of proteinopathies is that misfolded proteins "force" other normal proteins to misfold. This process has a prion-like spreading behavior. That is, one misfolded protein can spread throughout the cell and even outside the cell, causing proteins in other cells to misfold. This spreading behavior causes the disease to progress progressively throughout the brain [5]. In Alzheimer's and Parkinson's diseases, such spreading pathways are also observed by PET scans. Factors influencing the development of proteinopathies include genetic mutations, oxidative stress, inflammation, changes in the intracellular environment, and disruption of systems that control protein aggregation. Cells have various mechanisms to protect proteins from misfolding: chaperone proteins help repair misfolded proteins, and the proteasome system degrades these proteins. However, when these systems are overloaded or are not active enough due to genetic defects, misfolded proteins accumulate [6]. Current treatments are mainly aimed at relieving symptoms and do not address the root causes of the disease [7]. Therefore, new approaches, especially strategies aimed at stopping proteinopathies, are of great importance. Clinical trials of Dimebon began in 2008, and initial results showed that it was able to improve cognitive function

and slow the progression of the disease. This drug, unlike other existing drugs, helped to improve the overall condition of patients. Other clinical trials of Dimebon also confirmed its neuroprotective properties. These studies show that neurodegenerative diseases can be treated by stopping proteinopathies. This approach affects the underlying cause of the disease, slowing or stopping its progression. This strategy also serves as the basis for the development of new drugs. Early detection of proteinopathies makes it possible to slow down the disease process and improve the patient's quality of life [8]. Therefore, current scientific research is mainly aimed at identifying the preclinical stages of the disease before it manifests clinical symptoms. In this direction, research is being conducted on neurofilaments, volumetric changes in the brain and other biomarkers. Another important direction is the principle of personalized therapy. The causes of the development of the disease and the nature of protein accumulation may differ in each patient [9]. Therefore, in the future, treatment methods will be tailored to each patient's genetic profile, biomarker status and clinical manifestations. This approach will help to precisely target the disease and reduce side effects. The impact of lifestyle on proteinopathies is also being increasingly studied. A Mediterranean-style diet (olive oil, fish, vegetables), regular physical activity, brain-stimulating activities (reading, games, news), and social engagement are important factors in maintaining long-term cognitive health [10].

Conclusion: In conclusion, proteinopathies are complex pathological conditions that arise as a result of the accumulation of misfolded proteins and are mainly associated with neurodegenerative diseases. They disrupt the stability of the intracellular environment, increase oxidative stress, and lead to neuronal death. Today, various neuroprotectors, especially Dimebon, are being actively studied to slow down or stop this process. This drug and similar compounds play an important role by destroying pathological proteins, restoring mitochondrial function, and activating cellular defense mechanisms. This allows treating proteinopathies not only symptomatically, but also causally. In the future, research in this area may serve to introduce new treatment strategies into clinical practice. Early detection of diseases associated with proteinopathies, control of protein aggregation, and support of neuronal function will increase the possibility of preserving human health.

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