Protein Aggregates in Neurodegenerative Diseases

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Many neurodegenerative diseases are associated with protein aggregates. Misfolded proteins aggregate into a β-sheet structure, which is a major phenomenon of protein-misfolding diseases (PMDs). As a defense mechanism against misfolded protein aggregates, cells maintain homeostasis through two main modes of action: (i) refolding of misfolded proteins by molecular chaperones, and (ii) elimination of aggregated forms of pathogenic proteins as the first approach to alleviating neurodegenerative diseases. Decreases in these defense systems promote the deposition of aggregates leading to neurodegenerative diseases. The major neuronal proteins that cause PMDs include tau, α-synuclein, huntingtin, and β-amyloid.

Keywords: neurodegenerative disease ; protein degradation ; drug design ; ubiquitin-proteasome system ; autophagy ; protac

1. Overview

Neurodegenerative diseases, including Alzheimer's disease, Huntington's disease, and Parkinson's disease, are a class of diseases that lead to dysfunction of cognition and mobility. Aggregates of misfolded proteins such as β-amyloid, tau, α-synuclein, and polyglutamates are known to be among the main causes of neurodegenerative diseases; however, they are considered to be some of the most challenging drug targets because they cannot be modulated by conventional small-molecule agents. Recently, the degradation of target proteins by small molecules has emerged as a new therapeutic modality and has garnered the interest of the researchers in the pharmaceutical industry. Bifunctional molecules that recruit target proteins to a cellular protein degradation machinery, such as the ubiquitin–proteasome system and autophagy–lysosome pathway, have been designed. The representative targeted protein degradation technologies include molecular glues, proteolysis-targeting chimeras, hydrophobic tagging, autophagy-targeting chimeras, and autophagosome-tethering compounds. Although these modalities have been shown to degrade many disease-related proteins, such technologies are expected to be potentially important for neurogenerative diseases caused by protein aggregation. Herein, we review the recent progress in chemical-mediated targeted protein degradation toward the discovery of drugs for neurogenerative diseases.

2. Protein Aggregates

Many neurodegenerative diseases are associated with protein aggregates. Misfolded proteins aggregate into a β-sheet structure, which is a major phenomenon of protein-misfolding diseases (PMDs) [1]. As a defense mechanism against misfolded protein aggregates, cells maintain homeostasis through two main modes of action: (i) refolding of misfolded proteins by molecular chaperones, and (ii) elimination of aggregated forms of pathogenic proteins as the first approach to alleviating neurodegenerative diseases. Decreases in these defense systems promote the deposition of aggregates leading to neurodegenerative diseases. The major neuronal proteins that cause PMDs include tau, α-synuclein, huntingtin, and β-amyloid.

3. Protein Aggregates and Neurodegenerative Diseases

3.1. Tau

The tau proteins are abundant in neurons and play a role in maintaining the stability of microtubules in axons as the major microtubule-associated proteins (MAPs) [2]. The accumulation of aggregated tau is associated with synaptic dysfunctions, in which tau localization is abnormally shifted from axons to the somatodendritic compartment. Intracellular aggregates of tau, called neurofibrillary tangles, are found in patients with Alzheimer's disease (AD). Tau proteins become hyperphosphorylated and aggregate into neurofibrillary tangles [3]. Tauropathies, neurodegenerative disorders

characterized by the formation of neurofibrils of hyperphosphorylated tau, can also occur in atypical parkinsonian syndromes [4].

3.2. α-Synuclein

Parkinson's disease (PD) is a progressive nervous system disorder that affects the motor system [5]. It is caused by the degeneration of dopaminergic neuronal cells damaged by Lewy bodies, which are aggregates found in the cytoplasm of neurons. The key protein involved in Lewy bodies is an aggregate of α-synuclein. Lewy bodies affect various intracellular targets, including synaptic function [6], as α-synuclein regulates the mobility of synaptic vesicles and, consequently, neurotransmitter release.

3.3. Huntingtin

Huntington's disease (HD) is characterized by uncontrolled movements and cognitive deficits [7]. HD is an inherited progressive disorder caused by a CAG repeat coding for polyglutamine in the huntingtin protein, eventually forming a β-sheet amyloid structure [8]. Inclusion bodies formed by huntingtin are present in regions of the brain that degenerate [9]. Although the presence of huntingtin aggregates is not restricted to regions of the brain, the toxicity of the aggregates is limited to neurons in certain brain areas, such as the cortex and caudate [10].

3.4. β-Amyloid

AD is the most prevalent neurodegenerative disease and is characterized by amyloid beta (Aβ) deposition [11]. It is a progressive illness associated with loss of memory, task performance, speech, and recognition of people and objects. The disease is caused by two kinds of protein aggregates: (i) extracellular aggregates known as neuritic plaques composed of the Aβ peptide, which is derived from proteolytic processing of the amyloid precursor protein, and (ii) intracellular aggregates of the MAP tau [12]. These aggregates are known to be toxic to cells, although the mechanism of aggregation is only partially understood. Before forming insoluble fibrils, the pathogenic proteins aggregate into soluble toxic oligomers. The oligomers expose hydrophobic surfaces, thus disturbing the phospholipid bilayer [1].

4. Conclusions

Targeted protein degradation is a technology for artificially and selectively degrading intracellular target proteins using small- to intermediate-molecule compounds, which is a new drug modality that is completely different from conventional small-molecule drugs. The traditional drug development is based on the binding pockets of druggable targets. Occupation of small molecule inhibitors results in the loss of function of the target protein. However, these "occupancy-driven" pharmacology are limited by the absence of binding pockets of undruggable targets [13]. Overcoming the limitation of the "occupancy-driven" pharmacology, targeted protein degradation has shown that the loss of function of the target protein by removal of the target proteins is a result of the binding event. Because these chemical-mediated targeted protein degradation technologies work through the "event-driven" pharmacology, it has great potential to overcome problems associated with existing "occupancy-driven" pharmacology [13]. To date, several targeted protein degradation technologies have been developed, including PROTAC, molecular glues, and HyT, which achieve degradation by hijacking the UPS, as well as AUTAC, ATTEC, and LYTAC, which use the autophagy–lysosomal pathway as the degradation machinery. In particular, PROTACs have been proven to be efficient in degrading targeted proteins with >60 successful examples, two of which are currently in clinical trials focused on prostate and breast cancer treatment.

Neurodegenerative diseases have been defined as a group of intractable disorders that are characterized by progressive degeneration of neurons, resulting in neurological and psychiatric symptoms. Therapeutic targeting of protein misfolding and aggregation is currently being explored. Protein aggregates are considered to play a central role in the onset of neurodegenerative diseases [14]. Many neurodegenerative diseases are due to proteinopathies that result from aberrant protein aggregations and accumulations. To remove or prevent the formation of pathogenic protein aggregates in neurons or the brain, several approaches, such as the use of small molecules to inhibit protein production pathways, antibodies against target protein aggregates, gene silencing/suppression through RNA interference, and antisense oligonucleotides, are being intensively studied, some of which are being evaluated in clinical trials. However, the orally applicable small chemical approaches are more suitable for NDs than antibodies and oligonucleotide with potentially poor pharmacokinetic properties, although the CNS bioavailability still needs to be improved for this purpose. Cell permeability, tissue distribution, and pharmacokinetic properties can be improved using optimized cross-linkers of bifunctional molecules. Therefore, technologies for lowering the levels of pathological protein aggregates seem to have a significant potential in the treatment of neurodegenerative diseases in the future.

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