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Review

Nucleic acid aptamers for neurodegenerative diseases

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ABSTRACT

The increased incidence of neurodegenerative diseases represents a huge challenge for societies. These diseases are characterized by neuronal death and include several different pathologies, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's disease and transmissible spongiform encephalopathies. Most of these pathologies are often associated with the aggregation of misfolded proteins, such as amyloid-ß, tau, α-synuclein, huntingtin and prion proteins. However, the precise mechanisms that lead to neuronal dysfunction and death in these diseases remain poorly understood. Nucleic acid aptamers represent a new class of ligands that could be useful to better understand these diseases and develop better diagnosis and therapy. In this review, several of these aptamers are presented as well as their applications for neurodegenerative diseases.

Contents

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Abbreviations

AD	Alzheimer's disease
A-β	Amyloid-β
A-β_{40}	Amyloid-$\beta_{(1\text{-}40)}$
ALS	Amyotrophic Lateral Sclerosis
APP	Amyloid precursor protein
BACE1	β-secretase-1 enzyme
BBB	Blood Brain Barrier
CNS	Central Nervous System
DA	Dopamine
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
HD	Huntington disease
MS	Multiple sclerosis
NDs	Neurodegenerative diseases
PD	Parkinson disease
PrP^C	Normal cellular prion protein
PrP^{Sc}	Abnormal isoforms of prion protein
TSEs	Transmissible Spongiform Encephalopathies

1. Introduction

Since 1990, molecular evolution processes have been developed to isolate nucleic acid-based ligands. These ligands are usually named "aptamers" [1], from the Latin *aptus* meaning to fit, and the method to identify them is often known as "SELEX" for Systematic Evolution of Ligands by Exponential enrichment [2]. The SELEX has been extensively reviewed elsewhere [3–8]. Basically, a starting library of oligonucleotide sequences that contains a region of random base composition is synthesized. Sequences can be in natural DNA or RNA chemistry or in modified nucleic acids that can be incorporated by polymerases [9]. These modifications can be used to increase their resistance to nucleases (for instance 2′Fluoro, 2′Amino or 2′O-methyl) or to provide them with new binding capabilities (for instance providing hydrophobic groups). Then, the library is incubated with a target and the sequences that can bind to the target are extracted from the others before being amplified by PCR (or RT-PCR and *in vitro* transcription for RNA library). The repetition of incubation, partition and amplification steps leads to a Darwinian evolution of the library. The aptamer sequences with high affinity for the target are predominantly amplified, whereas the frequency of the others decreases in the library. Consequently, after several rounds of *in vitro* selection (usually approximately 4-15), aptamers can be identified by sequencing a sample of the library. Currently, it is even possible to use high-throughput sequencing to better analyse the enrichment of sequences during SELEX [10]. Nevertheless, it is well known that sequences that do not bind to the target could also be amplified by SELEX, for instance, sequences that are highly potent to be amplified by polymerases or that bind to the selection support. Therefore, sequences must be individually tested for binding in order to identify aptamers [11].

Aptamers can be selected against a wide variety of targets from small compounds (for instance vitamins, amino acids, or antibiotics) to macromolecules (nucleic acids structures, peptides or proteins). Usually, aptamers can bind to their targets with a dissociation constant K_d in the nM to pM range, but for small molecules their affinity is often lower with K_d in the μM range. Currently, several aptamers are already enrolled in clinical trials, and one is already approved for the treatment of age-related macular degeneration [12]. In addition to therapy, aptamers can rival antibodies for several applications including biosensors [13], purification processes [14] and diagnosis [15]. However, they present many advantages compared with antibodies. For instance, aptamers are less expensive and much more stable in long term storage, they seem to lack immunogenicity, and they can be chemically synthesized and easily conjugated, which make them ideal addressing moieties [16,17].

The use of aptamers can open new perspectives for neurodegenerative diseases (NDs). NDs include a wide range of pathologies and are very different in their causes and symptoms, which have in common the phenomenon of neuronal death. Some NDs are age-related, such as Alzheimer's disease, Parkinson's disease or tauopathies. Other diseases have genetic causes, such as the Huntington's disease or other causes such as multiple sclerosis or transmissible spongiform encephalopathy.

Some NDs are characterized by the progressive apparition and spreading of aggregated misfolded proteins in the brain, which is the case for Alzheimer's disease, Parkinson's disease, tauopathies, Huntington's disease and transmissible spongiform encephalopathy. The protein aggregation process involves misfolded proteins that become prone to self-association into small aggregates, which are sometimes called oligomers. Then, these aggregates can recruit additional monomers and extend through fibrillar structures. The accumulation of fibrils can form aggregation bodies of greater size that could be intracellular or extracellular. The link between the aggregation phenomena and neurodegeneration is generally poorly understood. For each disease, it is not clear which species in the aggregation process (the misfolded starting monomer, the oligomer or the final aggregation body) is toxic for neurons. Furthermore, the aggregation of one protein is not always specific to one disease and the aggregation of one protein could be found in different NDs. Accordingly, different pathologies associated with the aggregation of the same protein could be regrouped. For instance, different diseases associated with the aggregation of the prion protein could be regrouped as "prionopathies" [18], those associated with tau protein could be regrouped as "tauopathies" [19] and those associated with the aggregation of α-synuclein could be regrouped as "synucleinopathies" [20].

Aptamers selected for neurodegenerative diseases can have different applications [21,22]. Aptamers could be used for basic research to better understand the development of these diseases. However, they could also be used to develop new kinds of diagnosis or therapy. This review aims to provide an update on the literature in this field.

2. Aptamers for prionopathies

Several aptamers have been developed for "prionopathies", also named transmissible spongiform encephalopathies (TSEs) or prion diseases [23]. These NDs could affect animals (such as bovine spongiform encephalopathy or "mad cow") and humans (as Creutzfeldt–Jakob disease or kuru disease). The characteristic of TSEs is the conversion of a normal α-helix-rich cellular prion protein (PrP^C) into abnormal β-sheet-rich isoforms that are insoluble and resistant to protease K (PrP^{Sc}, Sc refers to "scrapie"). It has been demonstrated that the pathological three-dimensional conformation of these proteins could be transmitted not only between cells but also from one individual to another. This discovery allowed Stanley Prusiner to receive a Nobel Prize in 1997 because he showed that certain proteins could be infectious agents in the same way as viruses, bacteria and parasites. The means by which prions damage the host remains unclear, but some experiments have suggested a role for the PrP^{Sc} in neuronal dysfunction and death [24]. Aptamers have been selected against different prion proteins to study the pathology or set up sensors able to detect the protein