Journal of Biochemical Engineering & Bioprocess Technology

Opinion Article A SCITECHNOL JOURNAL

Targeting Amyloid Genic Proteins and their Emerging Role in Neurodegenerative Diseases

Wang Kosuke*

Department of Biochemical Engineering, University of Uppsala, Uppsala, Sweden

***Corresponding Author:** Wang Kosuke, Department of Biochemical Engineering, University of Uppsala, Uppsala, Sweden. E-mail: wang.jhon@gmail.com

Received date: 17 August, 2022, Manuscript No. JBEBT-22-73159;

Editor assigned date: 19 August, 2022, Pre QC No. JBEBT-22-73159(PQ);

Reviewed date: 31 August, 2022, QC No. JBEBT-22-73159;

Revised date: 16 September, 2022, Manuscript No. JBEBT-22-73159(R);

Published date: 30 September, 2022, DOI: 10.4172/jbebt.1000062

Introduction

Aptamers are oligonucleotides selected from large pools of random sequences based on their affinity for bioactive molecules and are used in similar ways to antibodies. Aptamers provide several advantages over antibodies, including their small size, facile, large-scale chemical synthesis, high stability and low immunogenicity. Amyloidogenic proteins, whose aggregation is relevant to neurodegenerative diseases, such as Alzheimer's, Parkinson's, and prion diseases, are among the most challenging targets for aptamer development due to their conformational instability and heterogeneity, the same characteristics that make drug development against amyloidogenic proteins difficult. Recently, chemical tethering of aptagens equivalent to antigens and advances in high-throughput sequencing-based analysis have been used to overcome some of these challenges. In addition, internalization technologies using fusion to cellular receptors and extracellular vesicles have facilitated central nervous system (CNS) aptamer delivery. In view of the development of these techniques and resources, here we review antiamyloid aptamers, highlighting preclinical application to CNS therapy.

Neurodegenerative diseases are characterized by a progressive loss of neuronal function. Most of these diseases are age-related and self-assembly of amyloidogenic proteins is thought to be a cause or a major deleterious mechanism in many of them. Examples include Alzheimer's disease (AD) and various other tauopathies, Parkinson's diseases (PD) and other synucleinopathies, prion diseases, and many other sporadic or genetic proteinopathies. The amyloidogenic proteins involved in these diseases are prone to self-association into neurotoxic oligomers and amyloid fibrils. In many cases, the oligomers, which have metastable structures, have been shown to play pivotal roles in the pathogenesis of the associated diseases and to be more toxic than the structurally stable fibrils. The abnormal protein assemblies cause neurotoxicity by a variety of mechanisms, including apoptosis, oxidative stress, inflammation, and disruption of proteostasis through blockage of proteasomal and lysosomal protein degradation. Given the significance of oligomers in the pathogenesis of many neurodegenerative diseases they have been the focus of attention as molecular targets of both diagnostic and therapeutic research and development. Therefore, generation of specific oligomer-binding reagents is a promising approach for development of early detection tools and redirecting the self-assembly process into dissociation back to nontoxic monomers, formation of nontoxic and nonamyloidogenic assemblies amenable to degradation, or in some cases, accelerating the aggregation process to reduce steady-state levels of oligomers in favor of less-toxic fibrils.

Amyloidogenic Proteins

Amyloidogenic proteins can be naturally structured or unstructured. Naturally structured proteins PrP undergo partial unfolding, whereas naturally unstructured proteins such as Aβ, αSyn, or tau, undergo partial folding under pathological conditions, initiating the self-assembly process. Both cases lead to formation of partially (un)folded monomers, which self-associate into increasing-size oligomers until a quasi-stable nucleus forms leading to the elongation phase. Elongation typically proceeds at a fast rate compared with the nucleation and may involve formation of quasi-stable high-molecular-weight oligomers, protofibrils, and eventually fibrils. Finally, the monomers are consumed and the system reaches a stationary phase in which no more growth is observed. Aptamers are molecular-recognition agents comprising single-stranded DNA or RNA oligonucleotides that similar to antibodies, bind specifically to diverse targets, including small molecules, peptides, proteins, and nucleic acids. Amyloidogenic proteins inherently tend to bind nucleic acids making it difficult to select aptamers specific for just one protein and even more so for distinct assembly states of these proteins. Nonetheless, aptamers offer several advantages compared with antibodies including their small size, facile chemical synthesis, including in large scale, high stability, and low immunogenicity, making them attractive for researchers aiming at developing molecular recognition tools for amyloidogenic proteins. Aptamers typically are obtained by selection from a random-sequence oligonucleotide library based on their affinity for the target of interest using a method called systematic evolution of ligands by exponential enrichment. The oligonucleotides usually span 30 to 100 nucleotides in length and their dissociation constants in complexes with their targets range from pM to mM. The sequence also contains constant regions required for enzymatic manipulation, such as PCR-primer binding and in vitro transcription.

A systematic survey by Dumontier, DeRosa, and their colleagues based on 492 published aptamer-related papers has found that the use of DNA aptamers is increasing compared with RNA aptamers. Each nucleic acid has its own advantages and limitations. DNA oligonucleotides are more stable than their RNA counterparts to enzymatic and chemical degradation and are therefore easier to work with. On the other hand, the presence of the 2′-OH in ribose, as opposed to deoxyribose, and the absence of the 5′-methyl group in uracil compared with thymine allow higher conformational stability of RNA, potentially increasing their affinity for the target The application of aptamers in the neurodegenerative-disease field has been reviewed in the past yet to our knowledge, there are no systematic reviews on aptamers targeting amyloidogenic proteins. The metastable nature of intrinsically disordered or misfolded proteins, which are prone to form toxic oligomers and eventually amyloid, makes these proteins one of the most challenging targets for aptamer generation. In the case of oligomers, the aptagens (equivalent to antigens) presented to the oligonucleotide library constantly change, whereas in the amyloid fibrils, the conformation of the aptagens can be both variable for the same protein due to formation of different strains and similar for different proteins in the core cross-β structure shared by most amyloid fibrils. Aptamers selected against amyloidogenic proteins can have various applications, including sensitive detection of biomarkers, as

selective inhibitors of the self-assembly process, and as tools for probing molecular mechanisms. The first application using aptamers as probes for biomarkers has been developing rapidly and is too large to include in this review. Therefore, we focus here on the challenges and potential solutions in this field and on preclinical therapeutic applications of aptamers specific for amyloidogenic proteins.

Artificial Technologies

To overcome the difficulty in selecting aptamers against metastable protein assemblies, approaches using stable mimics of these assemblies could be useful if the stabilized molecules represent accurately the metastable target. Here, we provide an update on the development of specific aptamers against amyloidogenic proteins, including amyloid β-protein (Aβ), tau, α-synuclein (αSyn) and prion protein (PrP). These proteins represent a range of sizes spanning an order of magnitude from 40- to 441-amino acid residues, and the two main mechanisms of initial misfolding and aggregation partial folding of an unstructured protein, such as Aβ, αSyn, or tau, and partial unfolding of a structured protein PrP. We discuss how bioinformatics-assisted approaches or artificial-intelligence-based technologies are used to assist the aptamer selection and optimization processes. We also examine approaches for analysis of the secondary and tertiary structures of aptamers and aptamer–target interaction and strategies for CNS-targeting delivery of aptamers for future development of therapeutics in neurodegenerative diseases. Although the selection of the RNA aptamers was against Aβ40 trimers, the final aptamers were not selective for trimers or other oligomers, but bound to Aβ40 fibrils and did not display a higher affinity for the fibrils than the naive oligonucleotide library used for the selection before enrichment. Part of the explanation of these results was that the PICUP immobilized Aβ40 trimers themselves might have aggregated during the selection process to form fibrillar structures. Further analysis suggested that oligonucleotides have a high, nonspecific affinity for amyloid fibrils, as KM33 and KM41 also recognized fibrils of other amyloid genic proteins, including calcitonin, islet amyloid polypeptide, insulin, lysozyme, and PrP106–126, which share a cross-β structure and fibrillar morphology with Aβ fibrils. Thus, Rahimi demonstrated that the aptamers could be used to monitor fibril formation in a similar manner to thioflavin T fluorescence.