Journal of Clinical Infectious Diseases & Practice

Short Communication Open Access

Multifactorial Conformational Diseases: Advancements in Multitargeted Therapeutic Interventions

Sargueil Bruno*

Department of Pharmacognosy, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt

Abstract

Neurodegenerative diseases such as Alzheimer's, Huntington's and Parkinson's diseases have multifaceted nature because of the different factors contributing to their progression. The complex nature of neurodegenerative diseases has developed a pressing need to design multitarget-directed ligands to address the complementary pathways involved in these diseases. The major enzyme targets for development of therapeutics for Alzheimer's disease are cholinesterase and β-secretase enzymes. Besides that, mitochondrial dysfunction, oxidative stress, and/or environmental factors strongly associated with age have also been implicated in causing neurodegeneration. After years of intensive research, considerable evidence has accumulated that demonstrates an important role of these factors in the etiology of common neurodegenerative diseases. Despite the extensive efforts that have attempted to define the molecular mechanisms underlying neurodegeneration, many aspects of these pathologies remain elusive.

Introduction

Neurodegenerative diseases are a group of debilitating conditions characterized by the progressive dysfunction and loss of neurons in the central nervous system. These diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis, share common pathological features such as the accumulation of misfolded proteins and the formation of aggregates [1]. The etiology of neurodegenerative diseases is complex, involving both genetic and environmental factors. In this article, we will explore the multifactorial nature of neurodegenerative diseases and discuss the latest therapeutic interventions being developed to tackle these challenging conditions.

Neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's diseases and amyotrophic lateral sclerosis (ALS) make up a group of pathologies characterized by separate etiologies with distinct morphological and pathophysiological features [2]. There is a huge body of evidence that suggest that these disorders arise by multifactorial conditions such as (a) abnormal protein dynamics with defective protein degradation and aggregation, (b) oxidative stress and free radical formation, (c) impaired bioenergetics and mitochondrial dysfunction, and (d) exposure to metal toxicity and pesticides. Although a lot of research has been carried out to understand the pathophysiology of these proteinopathies, still clarity in terms of viable drug targets is elusive. However, in order to explore applications directed toward developing recent emerging therapies for these diseases, neuroscientists have exploited the understanding of the basic etiology of these diseases. Although each disease has its own molecular mechanism and clinical manifestations, some general pathways might be recognized in different pathogenic cascades.

Understanding the Multifactorial Conformational Diseases

Neurodegenerative diseases are considered multifactorial conformational diseases because they result from the interplay of various factors, including genetic mutations, protein misfolding, impaired protein clearance mechanisms, oxidative stress, neuroinflammation, and mitochondrial dysfunction. These factors contribute to the formation of aberrant protein aggregates, such as beta-amyloid plaques in Alzheimer's disease and alpha-synuclein aggregates in Parkinson's disease [3].

Genetic factors play a significant role in neurodegenerative diseases. Mutations in specific genes, such as the amyloid precursor protein (APP) gene in Alzheimer's disease and the hunting tin gene in Huntington's disease, can lead to the production of misfolded proteins or an increased propensity for protein aggregation [4]. Additionally, variations in other genes, including those involved in protein clearance pathways and immune responses, can influence disease susceptibility and progression.

Protein misfolding is a common hallmark of neurodegenerative diseases. Normally, proteins fold into specific three-dimensional structures that are crucial for their proper function. However, under certain conditions, proteins can misfold and adopt alternative conformations, which can be toxic to neurons [5]. Misfolded proteins can seed the aggregation of other proteins, leading to the formation of large protein aggregates that disrupt cellular processes and trigger neuroinflammation.

Therapeutic Interventions

The multifactorial nature of neurodegenerative diseases poses significant challenges for developing effective therapies. However, researchers are making remarkable progress in identifying potential therapeutic interventions aimed at targeting various aspects of these complex diseases [6]. Here are some of the promising approaches being explored:

Disease-Modifying Treatments

Several drug candidates are being investigated to modify the disease progression by targeting the underlying mechanisms of neurodegeneration. These include approaches to reduce protein aggregation, enhance protein clearance pathways, and promote neuronal

***Corresponding author:** Sargueil Bruno, Department of Pharmacognosy, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt, E-mail: Brunosargueil@dl.edu.ey

Received: 02-May-2023, Manuscript No: jcidp-23-100132, **Editor assigned:** 05-May-2023, Pre-QC No: jcidp-23-100132 (PQ), **Reviewed:** 19-May-2023, QC No: jcidp-23-100132, **Revised:** 24-May-2023, Manuscript No: jcidp-23-100132 (R) **Published:** 31-May-2023, DOI: 10.4172/2476-213X.1000187

Citation: Bruno S (2023) Multifactorial Conformational Diseases: Advancements in Multitargeted Therapeutic Interventions. J Clin Infect Dis Pract, 8: 187.

survival. Examples include anti-amyloid antibodies in Alzheimer's disease and gene-silencing therapies in Huntington's disease [7].

Parkinson's Disease

Parkinson's disease (PD) is neurodegenerative disorder caused by loss of dopaminergic neurons in the substantia nigra, leading to bradykinesia, rigidity, tremor, and gait dysfunction. Expressing neurotrophic factors such as glial cell-derived neurotrophic factor (GDNF) were tested in a single clinical trial and neurturin (NTN) was investigated in three clinical trials in PD patients. The rationale for delivering these neurotrophic factors was not to target a causative pathological molecular pathway but to provide neurotrophic support to the degenerating neuronal population. Although AAV delivery of these neurotrophic factors was well-tolerated in patients, the efficacies are unclear. However, these studies were important to demonstrate the feasibility and tolerability of intraparenchymal delivery of gene therapy directly in the human brain.

Alzheimer's Disease

Alzheimer's disease (AD) is the most common cause of age-related dementia affecting more than 40% of individuals of 85 years and older. More than 100 therapeutic compounds have been tested to date, but all failed to positively modify the course of the disease. Most gene therapy clinical trials for AD are based on intracerebral delivery of AAV-NGF [8]. NGF encodes for nerve growth factor and is similar to GDNF and NTN in that it could provide neurotrophic support to neurons. Preclinical studies have shown that NGF can prevent degeneration of adult cholinergic neurons in the fore brain after injury. Although the surgical procedures and the treatments proved to be safe in humans, the efficacy of the studies was inconclusive.

Precision Medicine

Tailoring treatments to individual patients based on their genetic profiles is a promising avenue in neurodegenerative disease research. Genetic testing and biomarker analysis can help identify specific subtypes of diseases and guide personalized treatment strategies, enabling more effective and targeted interventions.

Neuroinflammation and Immune Modulation

Chronic neuroinflammation is a common feature of neurodegenerative diseases. Therapies aimed at modulating the immune response and reducing inflammation is being explored. This includes the use of anti-inflammatory drugs, immunomodulatory agents, and novel approaches to regulate microglial activation.

Proteostasis Enhancement

Strategies to restore protein homeostasis and promote proper protein folding are being pursued. This includes the development of small molecules that stabilize protein structures, chaperone proteins that assist in proper folding, and activators of the protein clearance pathways, such as autophagy [9].

Neuroprotective Approaches

Several therapeutic interventions aim to protect neurons from degeneration and promote their survival. These include the use of growth factors, antioxidants, and compounds that enhance neuronal resilience to stressors.

Future Perspectives

Gene therapy holds great promise for delivering therapeutic genes to treat neurological disorders. AAV vectors are currently considered one of the safest vehicles to treat CNS disorders. Several serotypes are available and as the potential of gene therapy is increasingly recognized, there is emerging need for new AAV serotypes. There is an enormous desire for new AAV vectors with improved transduction profile, better distribution, and higher transduction in the target organs upon less invasive administration routes. The genetic modification of AAV vectors and engineering AAV vectors could overcome these hurdles. The selection of appropriate delivery routes is also an important factor for the success of gene therapy. Currently, direct administration of AAV vectors into the parenchyma is preferred for efficient transduction of the CNS [10]. Although this route of administration is invasive, the advantages over injections into the venous system or other fluid-filled compartments are clear. Intra-parenchymal administration provides high concentration of the transgene in the target cells, high local transduction, less distribution to other organs, and lower risk for immune responses or toxicities due to AAV particles or ectopic expression of the transgene. Administration of AAV via systemic or intrathecal routes require higher doses which in turn increase the risk for toxicity. There is also a lot of room for improvement at the transgene level. For example, generation of new promoters and cis-elements, optimization of codons, and more efficient transgene design could improve efficacy and restrict expression in specific CNS cell types.

Conclusion

Neurodegenerative diseases are complex and multifactorial conformational diseases that pose significant challenges to researchers and clinicians. However, the understanding of these diseases has greatly advanced in recent years, leading to the development of innovative therapeutic interventions. While there is still much work to be done, the progress being made in targeting the underlying mechanisms of neurodegeneration brings hope for effective treatments that can slow down, halt, or even reverse the progression of these devastating conditions. Continued research and collaboration are essential to unravel the intricate mechanisms of neurodegenerative diseases and pave the way for successful therapeutic interventions in the future.

MTDLs represent effective tools in facing the unfathomable complexity of neurological disorder. The superior therapeutic profiles of MTDLs to single-target small molecules are attributed to the ability of MTDLs to target multiple major pathological cascades of neurodegenerative diseases. In this context, we are currently optimizing lead 3 as a potential AD therapeutic through dual AChE/BACE-1 inhibition in combination with a third target. Tailoring the identified lead compounds to iron-chelating ability and antioxidant activity is anticipated to result in favorable neuroprotective profile.

References

1. Geremia A, Biancheri P, Allan P, Corazza GR, Sabatino A (2014) Innate and adaptive immunity in inflammatory bowel disease. Autoimmune 13: 3–10.
2. Boltin D, Perets TT, Vilkin A, Niv Y (2013) Mucin function in inflammatory bowel disease. J Clin Gastroenterol 47: 106–111.
3. Johansson ME, Stovall H, Hansson GC (2013) The gastrointestinal mucus system in health and disease. Nat Rev Gastroenterol Hepatol 10: 352–361.
4. Chassaing B, Darfeuille-Michaud A (2011) The commensal microbiota and enteropathogens in the pathogenesis of inflammatory bowel diseases. Gastroenterology 140: 1720–1728.
5. Bergstrom KS, Kissoon-Singh V, Gibson DL, Montero M, Sham, Huang T et al. (2010) Muc2 protects against lethal infectious colitis by disassociating pathogenic and commensal bacteria from the colonic mucosa. PLoS Pathog 6: 148-150.
6. Johansson ME, Gustafsson JK, Holmen-Larsson J, Jabbar KS, Xia L, et al. (2014) Bacteria penetrate the normally impenetrable inner colon mucus layer in both murine colitis models and patients with ulcerative colitis. 63: 281–291.

7. Schwerbrock NM, Makkink MK, Buller HA, Einerhand AW, Sartor RB et al. (2004) Interleukin 10-deficient mice exhibit defective colonic muc2 synthesis before and after induction of colitis by commensal bacteria. Inflamm Bowel Dis 10: 811–823.

8. Atuma C, Strugala V, Allen A, Holm L (2001) The adherent gastrointestinal mucus gel layer: Thickness and physical state in vivo. Am J Physiol Gastrointest Liver Physiol 280: 922–929.

9. Ermund A, Schütte A, Johansson ME, Gustafsson JK, Hansson GC, et al. (2013) Studies of mucus in mouse stomach, small intestine, and colon. I. Gastrointestinal mucus layers have different properties depending on location as well as over the Peyer's patches. Am J Physiol Gastrointest Liver Physiol 305: 341–347.

10. Vaishnava S, Yamamoto M, Severson KM, Ruhn KA, Yu X, et al. (2011) The antibacterial lectin RegIIIgamma promotes the spatial segregation of microbiota and host in the intestine. Science 334: 255–258.