Roles of Non-Coding RNA in Alzheimer's Disease Pathophysiology

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Alzheimer's disease (AD) is a chronic neurodegenerative disorder that is accompanied by deficits in memory and cognitive functions. The disease is pathologically characterised by the accumulation and aggregation of an extracellular peptide referred to as amyloid-β (Aβ) in the form of amyloid plaques and the intracellular aggregation of a hyperphosphorelated protein tau in the form of neurofibrillary tangles (NFTs) that cause neuroinflammation, synaptic dysfunction, and oxidative stress. The search for pathomechanisms leading to disease onset and progression has identified many key players that include genetic, epigenetic, behavioural, and environmental factors, which lend support to the fact that this is a multi-faceted disease where failure in various systems contributes to disease onset and progression. Although the vast majority of individuals present with the sporadic (non-genetic) form of the disease, dysfunctions in numerous protein-coding and non-coding genes have been implicated in mechanisms contributing to the disease.

ncRNA circRNA miRNA siRNA piRNA lncRNA

1. Introduction

Alzheimer's disease (AD) is a chronic degenerative condition of the central nervous system (CNS) that manifests mainly as dementia. It is the most common form of dementia and affects memory and higher executive functions, including learning, comprehension, language, and judgment, generally without effects on consciousness. The exact pathophysiological mechanisms underlying the cause of AD are still unknown. It is, however, clear that AD is a heterogeneous disease with a multifaceted etiology that includes genetic, immunologic, and environmental factors acting in concert to dysregulate homeostatic mechanisms and propagate the onset and development of the disease.

The extracellular aggregation of beta-amyloid (Aβ) peptides and the intracellular accumulation of hyperphosphorylated tau protein within the CNS are the most widely studied and recognised pathological features in AD development, while neural network and vascular theories for AD onset and development are also being actively explored [1]. Oxidative stress, mitochondrial dysfunction, autophagy, non-coding RNAs, and neuroinflammation are other processes for which new evidence of their integral roles in AD pathogenesis is constantly being discovered, further strengthening the fact that the etiological factors involved in the disease process are heterogeneous and work in concert until the final disease pathway is fully established.

Non-coding RNAs (ncRNAs) are a diverse family of non-protein-coding RNA transcripts that, due to their critical regulatory actions in multiple biological processes and disease development, are potentially useful as therapeutic targets and biomarkers for a range of physiological and pathological conditions [2]. This family of RNA molecules includes microRNAs (miRNAs), long noncoding RNAs (lncRNAs), small interfering RNAs, circular RNAs (circRNAs), and piwi-interacting RNAs (piRNAs) that interact with other RNAs, DNA, and proteins through their primary sequence and structural elements. These ncRNAs regulate biological processes including transcription, RNA turnover, translation, and post-translational assembly of proteins [3][4]. As mentioned, ncRNAs have been reported to play pivotal roles in the pathophysiologic processes that promote the onset and development of many diseases, including Alzheimer's [5][6][7], and therefore represent potentially useful and novel therapeutic targets and disease biomarkers.

2. Important Pathophysiological Processes in Alzheimer's Disease

AD is a multifactorial disease condition that involves a wide range of pathogenic mechanisms. While the most prominent risk factor for AD is age, family history, variant ε4 of the apolipoprotein E (APOE-ε4) gene, hypercholesterolemia, type-2 diabetes mellitus, and traumatic brain injury are emerging as important and sometimes modifiable risk factors for the disease [8][9][10][11]. Genome-wide association studies (GWAS) have identified several gene loci that influence the risk of AD and include the presenilin genes, *PS1* and *PS2*, *clusterin*, *complement receptor 1*, *ABCA7*, *PICALM*, *CD33*, *MS4A6A*, *MS4A4E*, *CD2AP*, *SOAT1*, and *PTGS2* [12][13]. The products of many of these gene loci are known to influence the expression of proteins involved in Aβ degradation, CNS immune regulatory processes, and cholesterol metabolism, key processes that have been identified as modulators of inflammatory and neurodegenerative components of AD pathogenesis. A number of environmental factors have also been shown to play varying roles in AD pathogenesis. However, the exact mechanisms these factors play in AD onset and progression have not been fully elucidated [14].

The accumulation of Aβ and hyperphosphorylated tau protein is a well-studied pathologic endpoint of AD and is classically identified on histologic examination as senile plaques and neurofibrillary tangles (NFTs), primarily within the hippocampus, neocortex, and other subcortical regions of the brain. Senile plaques are extracellular deposits of the Aβ peptide that are produced via cleavage of the type I transmembrane amyloid precursor protein (APP). Cleavage of the APP by α-secretase, which represents the constitutive pathway of APP processing in neurons, generates a peptide referred to as p3 and precludes the formation of toxic Aβ. Under some physiological but mostly pathological conditions, cleavage of APP by β-site APP-cleaving enzyme 1 (BACE1) activates a pathway that involves the generation of a 99 amino-acid C-terminal fragment (C99) and a soluble fragment referred to as sAPP-β. C99 is further processed by the γ-secretase complex of proteins (PS1, PEN2, Aph1, and nicastrin) to produce Aβ of lengths varying in size from 37 to 43 amino acids, with those longer than 40 amino acids being more hydrophobic and aggregating. Researchers and others have demonstrated that levels of BACE1 protein and activity are increased in AD brain and cerebrospinal fluid (CSF) in the absence of changes in its mRNA [15][16][17][18][19]. The other protein component associated with AD pathology is the hyperphosphorylated form of the cytoskeletal

protein tau, which accumulates within neurons and axons to form NFTs, with various adverse effects on neurotransmitter transport, synaptic transmission, and the regulation of apoptotic mechanisms [20]. Physiologically, tau acts to stabilise the microtubular network by binding to microtubulin, thus maintaining the integrity of the neuronal cytoskeleton and mediating the axonal transport of neurotransmitters. Increased activity of protein kinases, including glycogen synthase kinase 3β (GSK-3β), perturbation of the mitogen-activated protein kinase (MAPK) pathway, and a concurrent reduction in phosphatase activity have been shown to contribute to the hyperphosphorylation of tau and its subsequent accumulation and loss of function [21][22].

Aβ is well known to induce synaptotoxicity. Studies by Talantova and colleagues [23] revealed that the binding of Aβ to nicotinic acetylcholine receptors on astrocytes promotes the release of glutamate, which in turn activates extrasynaptic NMDA receptors (eNMDARs) on neurons, with resultant excitotoxic effects manifested by a dampening of evoked and miniature excitatory postsynaptic currents (mEPSCs) within the hippocampus [23]. The binding of Aβ to astrocytic receptors results in a cascade of cyclical events that accentuate the generation of Aβ, resulting in the generation of nitric oxide and reactive oxygen species that culminate in cellular toxicity (reviewed by [24]).

Mitochondrial dysfunction and oxidative stress act in a reciprocal, mutually potentiating manner to promote the onset and pathophysiological progression of AD [25][26]. Electron leakage during ATP (adenosine triphosphate) generation by the electron transport chain within neuronal mitochondria leads to the sequential generation of toxic reactive oxygen species (ROS) and reactive nitrogen species (RNS), all of which promote the propagation of pathologic processes involved in the disease, including Aβ generation [27][28]. Conversely, Aβ has also been shown to be a potent inducer of oxidative stress and damage within neurons [24][29].

Neuroinflammation is another important and well-established pathologic factor in Alzheimer's disease onset and progression. Microglia are involved in the uptake and subsequent detoxification of Aβ and the mediation of various neuroinflammatory processes and pathways. During pathologic states, microglia may become overactive and undergo extensive functional and morphological changes, often resulting in the over-production of numerous pro-inflammatory cytokines and subsequent neuronal and synaptic toxicity and loss, with attendant over-production and accumulation of Aβ and tau, generating a vicious cycle of neurodegeneration [30][31]. Perturbations in cellular autophagic processes also promote the accumulation of Aβ and hyperphosphorylated tau proteins, resulting in further propagation of these toxic products [32][33].

3. Non-Coding RNAs: Introduction and General Regulatory Functions

The central dogma or tenet of molecular biology, as developed from studies of simpler organisms, is that DNA acts as a template for the transcription of messenger RNAs (mRNAs), which in turn serve as templates for the production of proteins via the processes of translation. Emerging research has consistently revealed an increasing number of exceptions to this rule, i.e., RNA types that do not encode for proteins, especially in more complex living organisms. These RNA molecules include the traditionally known classes of RNAs involved in translation, such as

transfer RNAs (those that carry amino acids and are involved in the synthesis of proteins), ribosomal RNAs (RNAs involved in forming the machinery for protein synthesis), small nuclear RNAs, which are involved in splicing events involving mRNA transcripts, and small nucleolar RNAs that are critically involved in the chemical modification of other smaller RNAs such as ribosomal and transfer RNAs. Non-coding RNAs are broadly classified as either housekeeping or regulatory ncRNAs. Regulatory ncRNAs have been categorised based on their length into short-chain ncRNAs that include circular RNAs, short-interfering RNAs, microRNAs, and piwi-associated RNAs, and long ncRNA (lncRNA) [34][35]. As the name suggests, regulatory RNAs act as important regulators of gene expression in many essential cellular systems and biochemical interactions. Long non-coding RNA refers to species longer than 200 nucleotides in length and is known to play roles in biological processes, including epigenetic control of chromatin modification, mRNA stability, promoter-specific regulation of genes, the inactivation/lyonization of X-chromosomes, and imprinting [3].

4. Roles of Non-Coding RNAs in Alzheimer's Disease Pathogenesis

A growing body of literature consistently implicates noncoding RNAs (ncRNAs), in particular miRNAs and lncRNAs, in AD pathogenesis. These ncRNAs have been shown to contribute via numerous pathways to amyloid-β (Aβ) peptide and tau accumulation, neuroinflammation, neuronal loss, and other known pathomechanisms by which AD states become established.

5. Prospects of Non-Coding RNAs as Potential Therapeutic Targets and Biomarkers for Alzheimer's Disease

The discovery of the roles that ncRNAs play in various pathogenic processes in Alzheimer's disease provides a new perspective for further understanding the disease process and developing new therapeutic options for the disease. Some of the numerous mechanisms by which non-coding RNAs influence the pathophysiological processes involved in Alzheimer's disease have been extensively discussed. These influences imply that non-coding RNAs can be employed, targeted for therapeutic benefits, or used as biomarkers for Alzheimer's disease.

Non-coding RNA-based therapies have already been developed for a wide range of disease conditions [36] and studies are ongoing to identify viable non-coding RNA therapeutic targets for Alzheimer's disease. MicroRNAs and long non-coding RNAs are two families of ncRNAs that have been best studied for their potential as therapeutic targets for Alzheimer's disease. Many of the studies suggest that ncRNAs can be manipulated, depending on their intrinsic contributions to AD pathophysiology, in order to slow down disease progression and produce beneficial clinical effects. The expression profile of non-coding RNAs in the brains of AD patients with respect to different pathological processes reflects their potential as therapeutic targets. The levels of a number of microRNAs are altered during specific Braak stages in AD patients, and changes in the expression of certain miRNAs are observed throughout the disease process, from early stages characterised clinically by mild cognitive impairment to the later, more clinically severe stages. As described in previous sections, the dysregulation of miRNAs in the brains of AD

patients and animal models affects the pathological progression of AD by regulating many target genes and signalling pathways and may be manipulated for therapeutic benefits in a wide variety of neurodegenerative conditions [37]. MicroRNA mimetic activity represents a new approach to miRNA therapeutics. They are exogenously synthesised double-stranded RNA molecules that are subsequently processed and modified in vivo into functional microRNAs [38][39]. Other miRNA mimics may be designed to inhibit the functions of endogenous miRNAs, and they are typically designed based on the complementary sequence of the target miRNA.

Long non-coding RNAs also exert significant influences on various pathophysiological processes in Alzheimer's disease, and therapeutic measures to target them are also being developed. Oligonucleotide compounds, antisense oligonucleotides, and small interfering RNAs are being investigated for their ability to target and knockout specific lncRNAs and harness therapeutic effects [40][41].

Oligonucleotides, antibodies, and other small molecules are also being explored for their ability to precisely target ncRNAs for therapeutic benefits [42]. These molecules can gain entry into cells and specifically target RNAs that are ordinarily not easily accessible to other types of therapeutic compounds or substances that rely on cell receptor activation [43][44]. The high specificity of oligonucleotides in binding RNA targets will also result in a significantly minimal side effect profile.

An important challenge that ncRNA-based therapy for Alzheimer's disease faces is the blood-brain barrier, and strategies such as lipid or polymer nanoparticle delivery systems [45][46], focused ultrasound [47], and adeno-associated virus vectors [48] are being investigated to circumvent this challenge.

Non-coding RNAs circulating in the serum or CSF are also potentially useful as biomarkers for the early detection of Alzheimer's disease based on the changes in their expression during the disease process [49]. A number of studies have identified the potential usefulness of specific miRNAs and piRNAs as diagnostic or prognostic markers for Alzheimer's disease. There are advantages to using circulating miRNAs as biomarkers apart from their close association with diseases: the ease of use of miRNA detection technology, the resistance of miRNAs to RNase digestion and tolerance of a wide range of pH conditions, and their stability at room temperature [50]. These advantages suggest the possibility of miRNAs and possibly other ncRNAs as ideal biomarkers for AD. Early diagnosis may bring about interventions that significantly delay or even prevent Alzheimer's disease onset, and more studies to identify rapid and non-invasive biomarkers must be embarked upon in order to improve early diagnosis.

A major phenomenon that should also be explored in future studies is the existence of different types of RNA fragments within protein deposits in AD. Shmookler Reis and colleagues [51] demonstrated a significant, non-random presence of RNA within pathological protein aggregates in AD states, and the significance of this finding needs to be studied in detail, especially as regards its cause and effects on AD pathophysiology.

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