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Deregulated MicroRNAs Associated With Alzheimer's Disease

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Article Info

Abstract

Alzheimer's disease (AD) is one of the most common neurodegenerative disorders caused by aging. Alzheimer discussed his findings on the brain pathology and symptoms of presenile dementia publicly on 3 November 1906, at the Tübingen meeting of the Southwest German Psychiatrists. The attendees at this lecture seemed uninterested in what he had to say. Following the lecture, Alzheimer published a short paper summarizing his lecture; in 1907 he wrote a larger paper detailing the disease and his findings. Kraepelin first named the disease as Alzheimer's disease in Handbook of Psychiatry in the chapter on "Presenile and Senile Dementia" in 1910. Dr. Alois Alzheimer, characterized the disorder with the presence of amyloid plaques and neurofibrillary triangle (NFT) in the patient's brain. Recently, studies exhibit that miRNA plays a role in moderating expression of the AD-related genes as well as subsequent phenotypic manifestation. Additionally, a number of studies indicate that miRNA is deregulated in AD human brain. In this review we focused on three aspects of the roles of miRNAs in the development of the Alzheimer's disease: 1) During the progress of the disease, miRNA's expression mutates and plays a pathological impact on the pathogenesis. Therefore, identifying and analyzing the expression of the microRNA will provide an insight on the pathogenic. 2) Since a single miRNA may have multiple gene targets in Alzheimer's disease it is necessary to identify differently expressed miRNAs (DEM) and differently expressed genes (DEG). 3) Since miRNA's target multiple genes through pathways, they make complex regulatory networks, and search of such networks allows better understanding and modeling the biological system of the disease.

1. INTRODUCTION

Alzheimer discussed first time his findings on the brain pathology and symptoms of presenile dementia publicly on 3 November 1906, at the Tübingen meeting of the Southwest German Psychiatrists. Following the lecture, Alzheimer published a short paper summarizing his lecture [1a]; in 1907 he wrote a larger paper detailing the disease and his findings [1b]. The disease would not become known as Alzheimer's disease until 1910, when Kraepelin named it so in the chapter on "Presenile and Senile Dementia" in the 8th edition of his Handbook of Psychiatry.

Alzheimer's disease (AD} is one of the most common neurodegenerative disorders caused by aging. With approximately more than 5 million patients diagnosed yearly, AD accounts for more than 80% of dementia cases worldwide. Moreover, it's also expected that by the year 2050, there will be one new AD case every 33 seconds [1]. Ever since AD was discovered by Dr. Alois Alzheimer, pathologist characterizes the disorder with the presence of amyloid plaques and neurofibrillary triangle (NFT) in the patient's brain, which suggests that these pathologies cause the disease. The accumulation of the amyloid plaque is due to extracellular deposits of Aβ in the brain parenchyma as well as the cerebral blood vessels commonly also referred as cerebral amyloid angiopathy (CAA). On the other hand, NFT's are aggregates of hyper-phosphorylated tau proteins. Patients that don't suffer from the aggregation of Aβ and NFT are not qualified to be AD, but instead are another type of dementia [2]. Furthermore, the aggregation of Aβ and NFT will lead to loss of the synaptic function, mitochondrial damage, as well as activation of microglia which will ultimately lead to neuronal death. Therefore, evidence emerged that neuroinflammation cascades that are caused by activation of the microglia play a role in the pathogenesis of AD. [3]. It was discovered, that activated microglia is found to be clustered around the Aβ plaques and NFT in AD. In healthy individuals, microglia is found to extinguish damaged neurons and pathogens, thus it has a phagocytic role. However, in AD, microglia is found to be proliferated, hence, it releases pro-inflammatory cytokines, chemokines and interleukins which in return causes neuroinflammation as well as damage to the tissue. Moreover, this features and highlights the pro-inflammatory cytokines that are released from microglia to attract attention for its role in AD [4].

Recently, evidence suggests that microRNA (miRNA) is a key player with an active role in the brain where it is involved in neural development and differentiation. Accordingly, 70% of the identified miRNAs are actually expressed in the brain. Thus, this class of non-coding RNA serves as a potential marker of neurodegenerative diseases such as AD. Hereafter, different studies exhibit that miRNA plays a role in moderating expression of the AD-related genes as well as subsequent phenotypic manifestation [5]. Additionally, a number of studies indicate that miRNA is deregulated in AD human brain. The most common deregulated miRNA's are found in Table 1.

Table 1: Most common deregulated microRNA associated with Alzheimer's disease.

microRNA	Dysregulation	Role
miR-9	Downreguled	-Targets FGFR1, NF-κB and SIRT1
miR-29	Downreguled	-Inverse relationship with BACE1.-Increases amyloid production [8]
miR-34	Upregulated	-Regulates p53 expression, associated with tau hyperphosphorylation
miR-92a	Downreguled	-Downregulation of JNK/c-Jun by targeting MKK4
miR-101	Upregulated	-Downregulation of MPK-1 which promotes activation of MAPK and IL-6, TNF-α and IL-1. [6]
miR-106	Downreguled	-Regulates expression of ABCA1, involved in production of ApoE [8]
miR-107	Downreguled	-Has a negative correlation with BACE1 and density of NFT plaques.-Targets BACE1, CDK5 and ADAM10 [8]
miR-124	Upregulated	-Downregulation of IL-6, iNOS and TNF- α-Upregulates TGF- β, aginase-1 and FIZZI [6]
miR-125	Upregulated	-Upregulation of MHC class II, CD40, CD80, CD86 by targeted IFR4. -Upregulates IFN-γ [6]
miR-146a	Upregulated	-Downregulation of CFH and IRAK-1.-Upregulation of IRAK-2 [9]
miR-155	Upregulated	-Targets SOCS-1 causing upregulation of iNOS, TNF-α, IL-6 and IFN-β-Targets SMAD2 and CEBPβ-Downregulation of CFH [6,8]
miR-181	Downreguled	-Regulates expression of SIRT1 [8]

Bioinfromatical analysis allowed the assumption that miRNA is able to regulate over 5,300 genes, which is around 30% of the human genes, which indicates that one miRNA is able to regulate about 200 genes [10]. There has been ~ 2,581 potential human miRNA recorded in miRBase. A single miRNA by itself exerts only a small effect on each single mRNA target, but however, the combined effect is significant and ends up producing measurable phenotypic traits. Regulatory processes that they are involved in include; proliferation, apoptosis, immune modulation, metabolic control, neuronal development, cell cycle, muscle differentiation, and stem cell differentiation. As a result, miRNA contain the ability of immediately switching between cellular programs and

because of that they are often referred as tiny master regulators of the human genome [11].

Even though a huge number of mammalian genes are targeted by miRNA's, the function of miRNA in the aspect of gene network is yet to be examined and studied. There are currently a wide range of bioinformatics tools that allow managing of miRNAs data flow. Throughout these tools, we are able to predict miRNA targets, validate miRNA findings, analysis of miRNA expression, identify regulatory networks of associated miRNAs, investigating metabolic and signaling pathway miRNA interplay and linking miRNAs to associated diseases [12, 13]. Accordingly, the aim of our study is to use in silico analysis tool to investigate the expression of miRNA in AD in order to determine their target genes. Furthermore, the goal is to indicate the possibility of using miRNA as a diagnostic biomarker in the early stage of Alzheimer's disease.

Specific Aims

1. To analyze Alzheimer's associated miRNA expression profile data.

MicroRNA are highlighted to be one of the most essential biomarkers in AD pathogenesis. This is due to the fact that during the progress of the disease, miRNA's expression mutates and plays a pathological impact on the pathogenesis. Therefore, identifying and analyzing the expression of the microRNA will provide an insight on the pathogenic.

2. To identify differently expressed miRNA (DEM) and differently expressed genes (DEG) in Alzheimer's disease.

As a single miRNA can have multiple gene targets, there are multiple in silico tools that allows us to predict miRNA targets and validate them. Such methods include TargetScan and miRanda, PicTar and PITA. [12,13].

3. To investigate regulatory network of AD associated miRNAs.

MiRNA's are correlated with different disease hallmarks thus they are found to have impact on different metabolic and signaling pathways and a possible transcription factor interaction. Further on, due to miRNA's role in targeting multiple genes and pathways, this allows multiple miRNA to make up a complex regulatory network. By constructing such networks it allows better understanding of modeling the biological system and the disease [12,13, 14].

Background Results

The emerging role of microRNA in neurodegenerative disorders is not only found affective in the study of AD but also in Parkinson's disease, amyotrophic lateral sclerosis and Huntington's disease. According to Goodfall et al. (2013), miRNA's are one of the most important discoveries in molecular biology. Recently, researches highlighted the alterations occurring in the miRNA's network that contributes to the pathophysiology of AD.

Several miRNA were found deregulated during AD, some of which directly affect Aβ production or by affecting the phosphorylation of tau, they are also found to impact the cytokines production by affecting both the innate and adaptive immune system [15].

However, due to the presence of numerous amount of miRNA's in the human genome, it is almost impossible to test and examine each miRNA's expression and how it targets different genes. Therefore, by using in silico methods and bioinformatics analysis, it allows us to conclude an idea on how miRNA deregulated expression may affect the disease and in what sense before experimenting it, which could be time consuming as well as expensive.

Furthermore, a study done in 2013 by Nie et al. (2003), aimed to identify different signatures of miRNA that are differentially expressed in HER2(+) versus HER2(-) in breast cancer, that may predict the status of the cancer and in return allows further idea on how to treat the cancer. According to their bioinformatics analysis, they identified that the target genes of the miRNA's are involved in important BP's such as angiogenesis, apoptosis, antiapoptosis, death, etc. Moreover, they recognized the signaling pathways that those DEM and DEG play an impact on. This aids in understanding the prognosis and predicted therapy that may be used to treat the malignant disease [16].

Another study done in 2014 by Hao et al. (2014), did a bioinformatics analysis on deregulated miRNA's and mRNA in Parkinson's disease. Additionally, they identified 200 dysregulated miRNA and 2,966 deregulated mRNA. Additionally, they predicted 304 target genes in total. Furthermore they identified that DGM are included in different biosynthetic processes and pathways, such as apoptosis, MAPK signaling pathways and other hallmarks that are known to play a role in the development of Parkinson's disease [14].
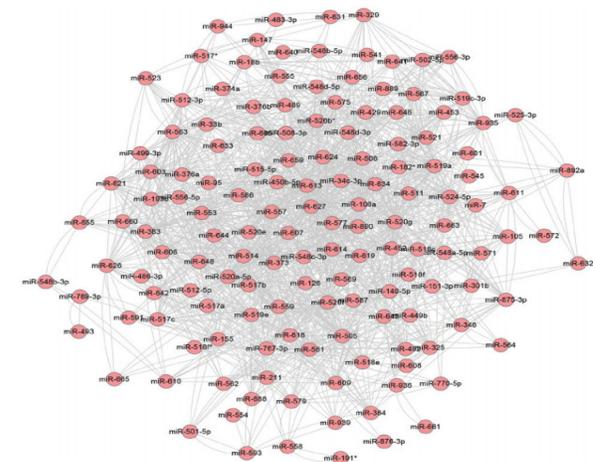

Figure 1: Interactome analysis of deregulated miRNA associated with Parkinson's disease.

Furthermore, in a systematic review and meta-analysis study done in 2016 by Hu et al. (2016), they reviewed 236 papers in order to investigate the deregulated miRNA's associated with AD. According to the fact that miRNA play an essential role in the neuronal development, it is logical to conclude that they may act as a biomarker in the pathology of AD. Thus, in their study they aimed to examine the diagnostic value of miRNA in AD in the CSF, hippocampus or in the serum. In their research, they identified more than 50 miRNA that are downregulated and expressed in the biofluid of the AD patient's brain. Following to that, they investigated the pathological processes of how these miRNA influence the pathology, results indicated that it plays a role on the APP metabolism, Tau pathology, neuroinflammation, and apoptosis. According to their meta-analysis results, they concluded that the quality of their results were good, as they found the sensitivity to be 0.86 and specificity to 0.87. Through these results, they assume that miRNAs may serve as a potential diagnostic tool for AD [17].

In another study done by Ghanbari et al. (2016), their aim was to identify miRNA related varients that can be associated with the risk of developing AD. They used the largest available genome-wide association study of AD. By studying 237 variants in 206 miRNA, they found rs2291418 variant found in the pre-miR-1229 sequence to be associated with the risk of developing AD. Throughout this variant, it impacted the structure and the expression of miR-1229. This further allowed them to reveal the target genes of the implicated miRNA in AD, which includes: SORL1, MCFD2, COL25A1 and BMP2 [18].

Accordingly, using in silico analysis to investigate and predict that pathways the miRNA interact and impact the pathophysiology of different diseases will allow saving of time as well as expanse. Moreover, as this study has not been investigated in Alzheimer's disease as of our knowledge, we aim to analyze and investigate miRNA's implicated in Alzheimer's disease via in silico analysis.

Experimental Design

Aim 1: To analyze Alzheimer's associated miRNA expression profile data.

•   Literature review of AD associated miRNA's collected from genomic and transcriptomic studies.

□   Genomic high throughput analysis: The miRNA expression profiles of Alzheimer's associated miRNA's will be obtained from Gene expression Omnibus (GEO) database (www.ncbi.nlm.nih.gov/geo). The GEO database stores and freely allows access of higthrough output genomic data submitted by the scientific community.

Aim 2: To identify differently expressed miRNA (DEM) and differently expressed genes (DEG) in Alzheimer's disease.

•   Based on the three most significant and efficient miRNA-target gene prediction algorithm, we will aim to predict the gene of targets of miRNA associated Alzheimer's. Accordingly, to reduce the false positive prediction that may occur, only genes with high confidence will be selected according to the exact predicted genes obtained from the three different tools.

□   TargetScan: TargetScan (http://genes.mit.edu/targetscan/) is a web tool that predicts the microRNA targets by looking into and searching through the conserved and non-conserved sites. In order to predict and find its targets in the 3'UTR of the protein-coding transcript it uses the base-pair rule. Throughout this program we will find information regarding miRNA-gene interactions.

□   PicTar: PicTar (http:// pictar.bio.nyu.edu) is another in silico analysis method that predicts miRNA targets through an efficient algorithm that uses the criteria of coexpression in space and time of miRNA as well as their targets. It predicts the targets by identifying the binding sites in a miRNA and multiple sites regulated by different miRNA's respectfully. By using pair-wise alignment algorithm it identifies conserved sites amongst multiple species.

□   miRanda: In order to find different genomic targets for microRNA, miRanda (http://www.microrna.org/microrna/home.do) is the optimum algorithm. It finds target sites by studying sequence complementarity between mature miRNA and the free energy of its target.

Aim 3: To investigate regulatory network of Alzheimer's disease associated miRNA's.

•   To analyze miRNA implicated pathways of regulatory co-expression network.

□   Database for Annotation, Visualization, and Integrated Discovery (DAVID) Knowledgebase: DAVID (https://david.ncifcrf.gov/home.jsp) is a method allows agglomeration of tens of millions of gene/proteins to produce high-throughput gene functional analysis.

□   Kyoto encyclopedia of genes and genomes Orthology-based Annotation System (KOBAS): KOBAS is another method that provides full functional analysis of the genetic pathways of the genes/proteins.

•   To predict and analyze construction of the regulatory co-expression network.

□   The Search Tool for the Retrieval of Interacting Genes (STRING): This in silico method will allow us to obtain a co-expression regulatory network found amongst

the miRNA's. Accordingly, Cytoscape software will be used to visualize the regulatory co-expression network throughout the potential relationship between miRNA and its target genes.

Expected Results

Analysis of miRNA profile expression in Alzheimer's patients should show different expression when compared to healthy samples. Additionally, miRNA profiling results should correlate with already identified deregulated miRNA in AD. We expect essential results that highlight different expressed target genes and interactome analysis that provide us with information regarding the different pathways that are associated with AD.

Conclusions

Alzheimer's disease(AD) is the most common type of dementia worldwide.Currently, AD has no cure and the ability to prevent it is limited.MiRNA expression has been linked to different pathological hallmarks in AD by inducing the innate and adaptive immune system.In silico prediction and analysis of microRNA in Alzheimer's disease would provide new insights in the prognosis and treatment of the neurodegenerative disease.

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