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A Review on Genes Involved in Alzheimer's Disease

Avneet Kaur*[1], Chinky Sharma[2], Durgesh Wadhwa[3], Deepika Arora[4], Ajay Bilandi[5]

[1]*Department of Pharmaceutical Chemistry, SGT University, Gurugram, Haryana, India*

[2]*Department of General Medicine, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, India*

[3]*Department of Chemistry, Sanskriti University, Mathura, Uttar Pradesh, India*

[4]*School of Biotechnology & Bioinformatics, Shobhit Institute of Engineering and Technology (Deemed to be University), Meerut, India*

[5]*Department of Pharmaceutical Sciences, RIMT University, Mandi Gobindgarh, Punjab, India*

ABSTRACT

It has been very well known that the protein's 3- Dimensional structure plays major role in maintaining biological functions. Their primary sequence codes for the relevant information required for their folding into 3-D structure either with the assistance or without the assistance of chaperones. In this case, the protein does not acquire its destined configuration, it may lead to several diseases and one of them is Alzheimer's disease (AD). AD is amongst one of most abundant neurological disorder which has global impact. In this the proteins and the genes involved in AD has been reviewed. It has been suggested by the scientists that the alterations in the β-sheet like motifs of proteins lead to the AD. Although change in β-sheet like motifs are common to protein misfolding, but misfolding from the α-helix to β-sheet is the property of amyloid deposits. Therefore, abnormalities in this conversion leads to the accumulation of unfolded or misfolded protein and production of insoluble fibrils. The abnormalities in the gene level has been discusses in this study.

Keywords:

Alterations, Disease, Folding, Gene, Misfolding, Protein

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Corresponding author: Avneet Kaur
e-mail ✉: avneet_fphs@sgtuniversity.org
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INTRODUCTION

Many cellular proteins rely on their 3-Dimensional configuration for action, which is obtained by folding the protein molecule encoded from the genome more specifically from the nuclear genome and from thirteen proteins present in mitochondria i.e. mitochondrial DNA. Alterations in a protein chain, whether caused by genetic or genetic variations or by irregular amino acid alterations, it may either alter the folding mechanism and cause protein misfolding. Since, consequences may vary based on [1] the protein's location, the cellular compartment wherein misfolding of protein happens, function of protein's degradation or the folding machineries, nearby genetic factors, and cell and an environmental factors. Results of mis-folding could be very different.

Misfolded proteins coexist with intermediately folded, unfolded, and properly folded present in the proteins in cells. Misfolded sequences of proteins present in the healthy cells either are correctly refolded or are degraded via chaperone proteins, which are engaged in protein trafficking, folding and intermediate stabilization. Indeed, most, if not all, proteins are now thought to be capable of forming amyloid fibrils under the right biochemical conditions. It has been demonstrated that many disorders are interlinked with the *amyloidogenic* proteins, on the other hand, have substantial domains of inherent disease in free soluble state and such specific, mostly small, internal sequence of amino acids and are unique, sometimes brief, internal sequences of amino acids which are both required and the sufficient for accumulation. Such kind of motifs can also be present in the non-disease proteins, whenever these fragments are released from the remainder of the protein, they assemble into cytotoxic amyloid fibrils.

Higher-level of amyloid accumulates are extremely resistant to deterioration once established. Proteasomes could only degrade single chain proteins and enable the polypeptides to be partly or completely unfolded (in the

case of proteasomes). Furthermore, due to the extensive connections formed between the protein polymers, the amyloid state is the highly thermodynamically stable. Amyloid aggregates' thermodynamic resilience also leads to their capacity to change primary structure of proteins to their amyloid forms (i.e., propagation like seed prion). Proteins may bypass a quality control mechanism of cell and then begins to assemble into a non-destined structures that may range from the amorphous assemblies and the oligomers to highly organized plaques as well as the amyloid fibrils under such situations of the cellular ageing, disease mutations or the proteotoxic stress.

Cells are usually exposed by steady stream of the misfolded proteins caused by biogenesis errors, disorder-creating mutations, and environmental stressors. They then refold, degrade, or sequester misfolded proteins in various compartments intracellularly like aggresomes or some other kinds of inclusion bodies. The protein chaperons combine with the emerging polypeptides when they arise from ribosomes and aid in their folding, as well as overseeing and participating in any stage of misfolded protein handling. Chaperones also have an eye on the consistency of the chains folded and, in some other cases, they may unfold and then re-follow them. Chaperones also keep an eye on the consistency of the folded chains and, in certain cases, it may unfold as well as refold the misfolded proteins. Conversely, the chaperones direct the misfolded protein to be degraded through ubiquitin mediated proteasome or autophagy linked pathway, or to be sequestered in the different compartments of cells.

Since a protein's free energy is determined via associations between its amino acid residues, minor changes in amino acid chain will alter nature of a landscape, potentially resulting in the development of novel local free energy minima or in development of the novel total free-energy minimum, leading to specific stable structure. This means that a protein's native state is not necessarily the global energy minimum. To expand definition of the energy folding settings to incorporate accumulation inclination, which can be exacerbated by extrinsic factors like high protein concentrations imagine a landscape of two deep valleys in the living cell [2]. Figure 1 depicts the definition. This may mean that aggregation states are stabilised in the steepest kinetic troughs. Since folding into an aggregation or native state results in stable geometries, such a choice may be justified by looking at how the two alignments relate to each other via inter - molecular as well as intra - molecular interaction.

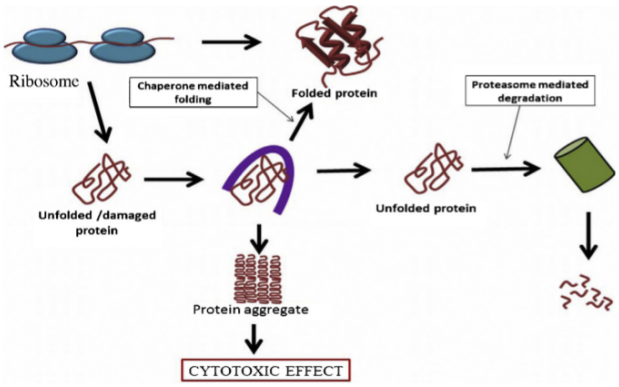

Figure 1: Protein misfolding and chaperone-mediated protein folding [3].

Primary neuropathological characteristic of the prion-related encephalopathies amd Alzheimer's disease is the extracellular aggregation of amyloidogenic proteins. Numerous experiments have shown that these aggregated proteins like prion protein and -amyloid (A), play a causal role in the growth of respective disorders. Protein accumulation is now thought to be implicated in other neurodegenerative disorders like amyotrophic lateral sclerosis, polyglutamine disorders and Parkinson's disease (PD), where the protein aggregates intracellularly. The likelihood of the general aetiology for such disorders focused on protein's misfolding is debatable, and the current studies appear to rule out a part for protein misfolding.

The likelihood of the general aetiology for such diseases focused on the protein's misfolding is still debatable, and current research seem to rule out a position for protein aggregation in disease's onset, even though it might appear essential for its full growth. It has been hypothesized that protein aggregation specifically disrupts the activity of the UPS (ubiquitin protease system), that is more proned to be associated with process of feedback mechanism which is basically positive feedback and is caused due to aggregation of protein, that in turn elevates the synthesis of the accumulated proteins [4]. As a result, the output of aggregated proteins improved.

Alzheimer's Disease (AD) can be defined as neuropathlogically described via intracellular cytoskeletal changes, neurofibrillary tangles, and a deposits in the parenchyma of brain and walls of the cerebral blood vessels. Neurodegenerative diseases, protein folding, and ageing are all linked by a similar pathogenic pathway. A protein is the most researched protein in the domain of AD pathogenesis because it's native -helix configuration is rapidly destabilized, causing it to follow a -sheet conformation As a consequence, insoluble, disease-creating aggregates of protein which occurs in the brain. Formation of deposits of A, that are insoluble fibrils of peptide A from 1 to 40 and 1 to 42, is the etiological process. The deposition of A, which are the insoluble fibrils of peptides of A from 1 to 40 and from 1 to 42, is an early occurrence present in the Alzheimer's disease, and also in various

biochemical, neuropathological, as well as laboratory findings point towards A playing a causative link in its pathogenesis. While mutations in the gene present in the encoding precursor protein of amyloid (APP) linked with the variant of AD (FAD) are exceedingly rare, they provide compelling proof that A is also involved. Therefore, contrary to intermittent AD, an improvement in A cerebral deposits is a typical occurrence in FAD triggered by mutations in three related genes: presenilin 1 (PS1), presenilin 2 (PS2), and APP.

DISCUSSION

Genetics of Alzheimer Disease

All in all, around more than 90% of individuals suffering with Alzheimer's disease tend to be intermittent, with onset ages ranging from sixty to sixty five years old (LOAD). Studies have shown that due to the existence of the load, there must be a biological explanation. No infectious gene has yet been discovered. Indeed, the APOE gene has been firmly linked to sporadic Lewy body disease across many genetic analyses (Table 1). Although this is true, new LOAD inherent and/or environmental triggers might potentially be discovered, as some carriers of the APOE-risk allele survive into their 90s. This study demonstrates that there might be 5 to 7 significant LOAD risk genes that yet to be replicated [5].

Genes Associated With Autosomal Dominant AD: Despite the fact that various 100 families have been amongst the above genes, which contribute for lesser than one percent of cases.

AD1: Amyloid precursor protein (APP): Scientists have isolated 40-residue constituent peptide (A) of plaque as well as of vascular amyloid deposits in 1980s, which contributed to APP type I integral membrane glycoprotein cloning through which the A is proteolytically extracted. The APP gene was at that point found to be located on chromosome 21q, which was previously unknown. The cloning of APP type I integral membrane glycoprotein from which A is extracted through proteolysis. The APP gene was then located on chromosome 21q, which explained why people with Down syndrome (trisomy 21) grow neuropathological characteristics and amyloid deposits, both of which are associated with AD in their 40. From then, 85 families have been found with over 32 related APP missense mutations. Surprisingly, the majority of these alterations are found on exons 16 and 17 near secretase sites for cleavage (Figure 2).

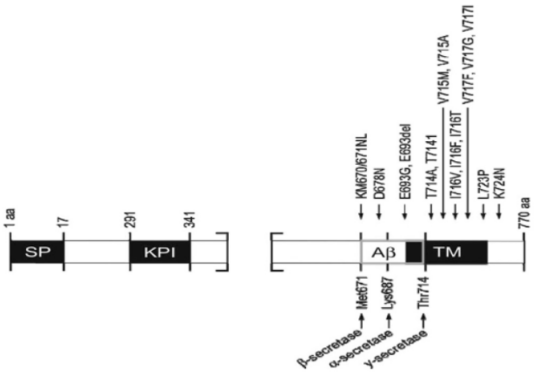

Figure 2: Structure and Mutations in Amyloid precursor protein (APP) [6].

AD3: Presenilin 1 (PSEN1): The results of linking and positioning cloning tests identified the presence of an AD3 region of chromosome 14, and PSEN1, which encodes for just a polytopic membrane protein, showed abnormalities in the presenilin 1 (PSEN1) gene. Atypical aspartyl protease-cleaving APP clusters have a large presenilin subunit. The most prevalent cause of EOFAD is due to mutations in the PSEN1 gene [7]. Because of mutations in the PSEN1 gene, 18% to 50% of autosomal recessive EOFAD cases are caused by missense mutations. It has been shown that over 176 unique PSEN1 variants have been found in families consisting of over 390 individuals. Mutations in PSEN1 result in an increased ratio of A42 to A40, which leads in reduced - secretase action (Table 1). It has been postulated that A42 deposition occurs in PSEN1 missense mutations before to the onset of clinical symptoms.

Table 1: Genes Associated with AD [8].

GENE NAME	GENE SYMBOL	CHROMOSOMAL LOCATION	AD LOCI	IINHERITANCE
Amyloid precursor protein	APP	21q21	AD1	Autosomal Dominant
Apolipoprotein E	APOE	19q13.32	AD2	Sporadic
Presenilin 1	PSEN1	14q24.2	AD3	Autosomal ominant
Presenilin 2	PSEN2	1q42.13	AD4	Autosomal ominant

AD4: Presenilin 2 (PSEN2): In 1995, researchers discovered a new gene present on chromosome 1 known as presenilin 2, which had high similarity with the AD3 locus in Volga German AD kindreds (PSEN2). A missense mutation in the PSEN2 gene, as opposed to a point alterations present in PSEN1 gene, is a rare cause of EOFAD, with increased frequency in people of European descent. PSEN2- effected families have clinical features that differ than those of PSEN1-affected groups apart from age of beginning of the afflicted family members. Those members of the family often begin having symptoms between the ages of 45 and 88. Additionally, the onset of age ranges widely for those afflicted by PSEN2.

Moreover, the onset of age varies widely amongst PSEN2-affected family members, but it is quite ~requent among family with PSEN1mutations, and the onset of age is

relatively comparable in families with various mutations. Changes in other genetics or environmental conditions may reduce the impact of missense alteration in the PSEN2 gene.

Genes associated with risk in sporadic AD

AD2: APOE: Several experiments have been conducted in which persons of different ethnicities have been connected to both in intermittent and familial late-onset Alzheimer's disease, which is the result of a APOE gene. The APOE 4 gene is associated with a higher occurence of Alzheimer's disease, which occurs at an earlier age in people with Down syndrome and mouse models expressing human APOE4, and an overall worse outcome after brain damage and stroke in both people and animals. The frequency with which APOE 4 allele ranges among ethnic groups, but then regardless of ethnicity, percentage of APOE 4 carriers is greater in healthy controls than in those with Alzheimer's disease.

There is no proven cure for Alzheimer's disease at the moment. Many researchers attribute this to fact that the condition cannot be clinically identified until well after biological onset of disease, when hallmark signs such as forgetfulness emerge. However, the inherent brain injury may have already progressed and been permanent at this stage. It takes between 15 and 20 years for misfolded amyloid protein to develop in people with AD. A buildup of misfolded proteins accumulates in the brain, causing the formation of amyloid plaques. An Austrian scientist, Dr. Klaus Gerwert, developed a method to detect misfolded amyloid peptides in blood plasma.

Researchers previously shown that changes in amyloid present in blood can be detected several years even before clinical occurrence of illness occurs. They also discovered that the presence of misfolded amyloid-present in the blood coincides with the forming of plaques in brain. The researchers decided to see how amyloid- would be used to assess the likelihood of developing Alzheimer's disease, as well as how the risk predictor compares to other identified and suspected risk factors.

In order to do so, they reevaluated blood samples obtained as part of ESTHER, a cohort study headed by Hermann Brenner and co-sponsored by the Saarland Cancer Registry, conducted a cohort analysis. The cohort research was started in the year 2000. The study examined the original blood tests of 150 ESTHER participants who were later diagnosed with dementia over the 14-year follow-up phase. These specimens were contrasted to those of 620 randomly chosen control subjects who were not considered to have dementia and who matched with the dementia subjects in terms of age, gender, and level of education.

Subjects in A misfolding had a 23-fold elevated risk of being diagnosed with Alzheimer's disease over 14 years. The study found no elevated risk in people with other forms of dementia, for instance, those affected by a decrease in blood flow towards the brain, proving Alzheimer's disease specificity.

The researchers have considered a specific version of the gene for apolipoprotein E (APOE?4), as well as pre-existing conditions (high blood pressure, diabetes, depression) or lifestyle causes, in their study (level of education, bodyweight). Excluding APOE4 status, which demonstrated a 2.4 times increased risk of all those who later developed Alzheimer's disease, none of the conditions tested associated with disease risk. It made no difference if the interval between the blood sampling and the clinical onset of dementia was in the range 0-8 or 8-14 years in estimating the likelihood of illness.

AD Aβ Peptide Generation: This considerable body of research says that amyloid A protein, which forms the major element of the amyloid plaques present in brain, is the root cause of the underlying pathologies that lead to Alzheimer's disease. It is synthesised by successive proteolytic cleavage of the APP, which ranges among 38 and 43 residues. Within neuronal cells, APP has three usual isoforms: APP695, APP751, and APP770. Depending on the protease that was present, the next step is to break down APP, which results in either non-amyloidogenic A formations or amyloidogenic A forms (disease-related). When secretase enzyme (a BACE1-specific enzyme) reaches the former phase, it cleaves APP among residues M671 and D672. Monomeric A peptides of varying lengths come from anterior pharynx-defective-1 (APH-1), PS1 or PS2, nicastrin, and presenilin C-terminus forming a secretase complex consisting of PS1 or PS2, nicastrin, and APH-1, which, after that, results in monomeric A peptides of varying lengths.

Oligomerization of Aβ peptide in AD: Enhancer-2 (PEN-2) cleaves the residual fraction of membrane bound APP at the For several years, intensive research has been undertaken to detect and improve quick, low-cost, and effective blood-based biomarkers for the diagnosis of Alzheimer's disease (AD). This study based on assessing -amyloid (A), which is recognized as one of the pathologic hallmarks of Alzheimer's disease, only to find inconsistencies between AD groups and non-AD control groups. In vivo, AβOs may be extracellular, residing in CSF and interstitial fluid. As previously discussed, when certain brain cells are exposed to extracellular AβOs in an experimental setting, they become unstable and deteriorate [11]. How AβOs cause the pathological alterations as well as why only the certain cells are influenced by basic questions that have yet be satisfactorily answered.

To boil it down, oxidative damage is produced when amyloid β oligomers (AβOs) and neuron membrane interact with one other. AβOs have indeed been reported to pierce lipid bilayers, initiating damage by functioning as a pore.

Molecular scale membranes modeling has lately been examined in the context of lipid membranes connections, which includes the possible involvement of metals. Although AFM imaging has only just gained widespread use, it has long been utilised to illustrate internal injuries to the POPC/POPS lipid bilayers caused due to the A40 in some different accumulation stages. In A peptides

cultured in the presence or absence of entire lipids present in brain extraction bilayers, A28 and A12–24 disrupt bilayers, whereas A40 does not. A oligomers are more susceptible to membranes than to monomers.

Prospective oligomers of A which have already been pyroglutamate-modified associate with neurons and cause membrane permeability disruption. A42 monomers but just not A40 oligomers were shown to generate ion channels owing to pore-causing beta-barrel AβO structures. Based on the certain findings, AβOs with a molecular weight larger than trimers lead to Ca++ entrance when they pass cell membrane. The zinc-sensitive Ca++ inflow that has been hypothesised as a possible lipid raft connection is promoted by the establishment of an annular octameric channel of A22–35, that has an annular channel core composed of 8 rings that induces a Ca++ influx, according to research findings [12]. The positioning of AβOs to the rafts is constant with the observations that the ganglioside GM1 depletion blocks the toxicity of AβO interactions.

Evidence, on other hand, indicate that a modest rise in membrane cholesterol levels may defend against AβO toxicity. A pentapeptide present in the glycine zipper region of A's C-terminus also protects by blocking visible membrane insertion and eliminating synaptotoxicity. The failure of the bilayer insertion theory to result for the specificity of AβO binding is a major challenge. When two neurons are placed side by side, their capacity to aggregate AβOs can be totally different, with one displaying robust synaptic aggregation and the other showing practically zero. This binding correlates with cell-specific toxicity as determined by tau hyperphosphorylation.

Accounting for binding saturability is also problematic, but it may be proposed that AβO injection into the lipid rafts which is unique to particular synapses might be storable. It has also been proposed that AβOs can function through proteins and lipids, leading to pores throughout their membranes whereas it is also attaching to receptors to trigger specific intracellular results. According to the receptors theory, AβOs are kind of ligands associated with gain-of-function ligands which are pathogenic which link inadvertently to the particular polypeptides that serve as the toxin receptors. Overall, this theory of receptor offers framework which is consistent with the key aspects of the cell-based evidence. Theory was proposed to understand cell-specific toxicity which was based on Fyn expression, as well as why AβO binding was practically abolished by manipulating cell surfaces with smaller concentrations of trypsin. Compatible with the receptor theory, AβO binding exhibits (A) saturation and strong affinity for the neurons cultured and the synaptosome formulations; (B) sensitivity for specific neurons and brain regions; and (C) synaptic targeting; (D) aggregation at dendritic spines; (E) inflammatory effect, like hyperphosphorylation of tau, particular to neurons with bound AβOs; and (F) sensitivity to low doses.

CONCLUSION

These results extend to both brain-derived as well as synthetic AβOs in general, and they obtain the theory that the AβO attachment is ligand-like and regulated by the proteins functioning as receptors of toxin inadvertently. In hippocampal cultured cells, AβO binding sites were found to be co-localized with NKA3. As will be addressed later, NKA3 down - regulation can play an important role in translating AO bonding into cell pathology. The AβO theory for AD pathogenesis has gained substantial popularity and recognition, as shown by the elevating number of publications regarding AβOs present in the last five years, and that the accuracy of information suggesting a toxic function of AβOs. As a result, the number of AβO-targeting therapeutics in the Alzheimer's disease pipeline has started to rise. We conclude that the growing interest in AβO targeting would be helpful to the care and diagnosis of Alzheimer's disease. Given the data for an AβOs involvement in disorders other than Alzheimer's, these measures may theoretically reach a larger percentage of the population. Finally, in order for these measures to yield clinical and diagnostic results, further research must be conducted.

Further advancements in AβO structure-function studies are needed for these activities to yield therapeutic and diagnostic benefits. Increasing investments in this and other AβO research would allow crucial gaps to be closed, paving the way for a smoother and shorter journey from bench to bedside.

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