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ROLE OF GENOMICS AND PROTEOMICS IN ALZHEIMER'S DISEASE

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Abstract

Alzheimer's disease (AD) is a complex neurodegenerative disorder characterized by progressive cognitive decline, and its underlying mechanisms involve intricate interactions between genetic and proteomic factors. Genomics and proteomics play a crucial role in understanding Alzheimer's disease by identifying genetic risk factors. Recent advancements in genomics and proteomics have enabled researchers to develop deeper into the molecular pathways implicated in AD. Genomic studies have uncovered various genetic variants associated with increased risk for AD, particularly in genes such as APP, APOE, TREM2, CLU, CD33, PSEN1 & 2 proteins like Aβ, Tau.

Our current understanding of AD pathologies involves various hypotheses, such as the cholinergic, amyloid, tau protein, inflammations, etc.

Keywords: Alzheimer's disease, Genes (APP, APOE, CLU, TREM2, CD33, PSEN1&2), Proteins (Aβ, Tau).

INTRODUCTION

Genomics

Genomics is the study of an organism's entire genome, including all its genes and how those genes interact with each other and their environment. The genome contains the organism's complete set of DNAs and is embedded in nearly every cell of that organism.

Father of genomics is FREDERICK SANGER. [1]

Proteomics

Proteomics is the large-scale study of proteins, particularly their structures and functions. It involves the analysis of the entire set of proteins (the proteome) expressed by a genome, cell, tissue, or organism at a specific time under specific conditions. [2]

Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by predominant impairment of neurons and formation of amyloid plaques, hyperphosphorylated tau protein & neurofibrillary tangles in brain. It is named after Dr Alois Alzheimer, who first described the condition in 1906.

Pathophysiology

Neuroinflammation

Neuroinflammation is thought to play a significant role in the development and progression of AD, alongside amyloid plaques and neurofibrillary tangles.

It is characterized by the activation of microglia, the brain's resident immune cells, and the release of pro-inflammatory cytokines and other inflammatory mediators. Neuroinflammation can lead to neuronal damage, synaptic dysfunction, and cognitive decline.

Mitochondrial dysfunction

Mitochondrial Dysfunction and AD Pathogenesis:

Impaired Energy Metabolism

Increased Oxidative Stress

Mitochondrial DNA and Genome

Beta-Amyloid Accumulation

Mitophagy Deficits

Mitochondrial dysfunction in AD is apparent from a decrease in neuronal ATP levels, which is associated with the overproduction of ROS, and indicates that mitochondria may fail to maintain cellular energy. A substantial amount of ATP is consumed in the brain due to the high energy requirements of neurons and glia.

Cholinergic insufficiency

Cholinergic insufficiency occurs when there is a deficiency in the neurotransmitter acetylcholine (ACh) at the synapse, often due to decreased production, impaired release, or excessive breakdown of ACh, which can be caused by various factors including neurodegenerative diseases like Alzheimer's, certain medications, nutritional deficiencies, or damage to the cholinergic neurons in the brain.

Autophagy dysfunction

Autophagy dysfunction is a key factor in the development of Alzheimer's disease (AD). Autophagy is a process that removes damaged organelles and protein aggregates from cells. When autophagy is impaired, proteins like amyloid beta and tau build up, which can lead to neuronal death. [3]

Genes involved in Alzheimer's disease

1.Role of Amyloid Precursor Protein in Alzheimer's disease

Amyloid precursor protein (APP) is a transmembrane glycoprotein which is a large precursor molecule produced by brain neurons, vascular & blood cells (platelets), less in astrocytes.

APP has many functions including synaptogenesis & synaptic plasticity, as a growth factor, in metabolism of CNS and peripheral tissues, as a metal binder (Cu) etc.APP is activated by proteolytic cleavage to generate A β peptides these peptides accumulate in the brain of people with AD to form amyloid plaques.

APP undergoes amyloidogenic pathway (toxic pathway) & non amyloidogenic pathway (non-toxic pathway).

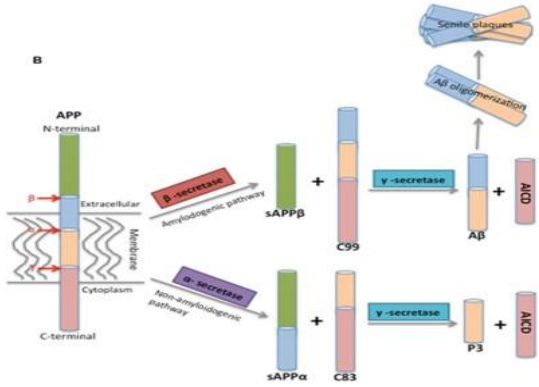


Fig no.1 Representation of Amyloidogenic pathway &Nonamyloidogenic pathway

Amyloidogenic Pathway

The APP in the presence of β secretase [β-site amyloid precursor protein cleaving enzyme1 (BACE-1)], is cleaved into soluble amyloid precursor protein beta (sAPPβ) & C99 which in turn in the presence of γ secretase (PSEN-1 & 2) produces A β peptides & APP intracellular domain (AICD).

The A β peptides undergo polymerization & oligomerization to form senile plaques or amyloid plaques(toxic).

The accumulation of these amyloid plaques leads to Alzheimer's disease.

Beta-site amyloid precursor protein cleaving enzyme 1(BACE1).

Non-amyloidogenic Pathway

The APP in the presence of α secretase enzyme undergoes cleavage to form soluble amyloid precursor protein (SAPPα) and C83 which in turn undergoes cleavage in the presence of gamma secretase to form P3 (nontoxic) & AICD.

Increasing the non-amyloidogenic pathway could be an effective treatment for Alzheimer's disease (AD). This could be done by activating α-secretase or inhibiting the amyloidogenic pathway with ß secretase inhibitors.

APP mutation

Mutation in the APP gene can cause FAD. These mutations can change the location of APP from the cell surface to early endosomes. They can also accelerate the generation of A β by increasing the A β 42/40.

Inheritance – Mutations in APP gene are transmitted through autosomal dominant inheritance.

APP gene can mutate in no. of ways that contribute to Alzheimer's disease:

Mutations in the amyloid precursor protein (APP) gene can occur in several ways, including:

Amino acid substitutions

A common mutation replaces the amino acid valine with isoleucine at position 717 of the protein. This mutation can lead to an increase in the amount of amyloid β peptide or to the production of a longer and stickier form of the peptide.

Mutations at the β'-cleavage site

Mutations at the β'-cleavage site can block the site and shift cleavage of APP to the β-site, causing increased Aβ production. For example, the E682K mutation is located at the β'-site and blocks it, causing increased Aβ production.

2.Presenilin - 1 & 2(PSEN-1&2)

PSEN-1 is expressed more broadly & present at the cell membrane. Most mutations are simple missense mutations.

It is located on chromosome 14q24.3

PSEN-2 is present mainly in late endosomes & lysosomes. The mutations are of small deletions, insertions or splice mutations.

It is located on chromosome 1q42.13

PSEN-1&2 encode the major component of gamma secretase enzyme which is responsible for sequential proteolytic cleavages of APP & the subsequent formation of A β peptides.

Mutations in PSEN-1 can alters neurogenesis which leads to premature agent phenotype with a reduce abundance of new born neurons in brain of people with AD. [4][5]

3. Clusterin (CLU)

Clusterin (CLU) plays a neuroprotective role by binding Aβ and facilitating its clearance.

Defects in these clearance pathways may lead to Aβ accumulation, contributing to neurodegenerative diseases like Alzheimer's disease

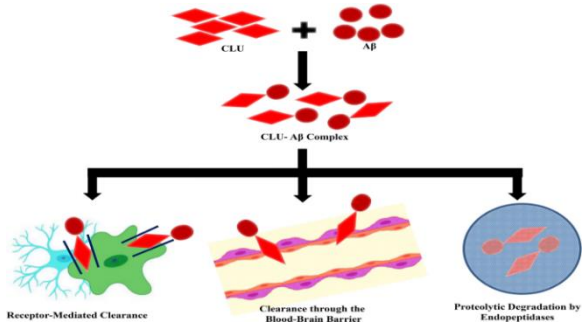


Fig no. 2 Clusterin-Mediated Clearance Pathways of Amyloid-Beta (Aβ)

1.Formation of CLU-Aβ Complex

Clusterin (CLU) is a glycoprotein that binds misfolded or aggregation-prone proteins, including Aβ, to prevent toxicity.
Amyloid-beta (Aβ) is a peptide that aggregates into plaques, contributing to neurodegeneration in Alzheimer's disease.
CLU binds to Aβ, forming a soluble CLU-Aβ complex, which prevents Aβ aggregation and facilitates its clearance

2. Clearance Pathways of the CLU-Aβ Complex

Once the CLU-Aβ complex is formed, it follows three main clearance mechanisms leading to different pathways:

(a) Receptor-Mediated Clearance

Specialized brain cells, such as astrocytes and microglia, express receptors that recognize the CLU-Aβ complex.

The complex is internalized through endocytosis, leading to intracellular degradation. This mechanism helps in removing Aβ from the extracellular environment, preventing its accumulation and toxicity.

(b) Clearance through the Blood-Brain Barrier (BBB)

The blood-brain barrier (BBB), composed of endothelial cells lining blood vessels.

The CLU-Aβ complex can be transported across the BBB into the bloodstream for systemic clearance.

This pathway is crucial for maintaining low levels of Aβ in the brain and preventing plaque formation.

(c) Proteolytic Degradation by Endopeptidases

The complex is subjected to degradation by endopeptidases, which are enzymes that break down proteins.

Enzymatic degradation of Aβ reduces its aggregation potential, thereby reducing neurotoxicity. [6]

4.CD33 Gene

The CD33 (Cluster of Differentiation 33) gene encodes a transmembrane receptor primarily expressed on immune cells, including microglia in the brain. It plays a key role in regulating neuroinflammation, which is a major contributor to Alzheimer's disease (AD).

It is located on Chromosome 19q13.41, Which is found on the surface of microglia and other immune cells. It is highly expressed in brain microglia, as well as in blood and bone marrow cells.

CD33 is a sialic acid-binding immunoglobulin-like lectin involved in:

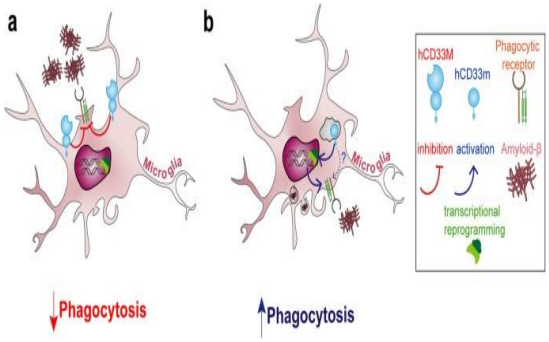
CD33 primarily functions as an inhibitory receptor, dampening microglial activation to prevent unnecessary inflammation. However, in AD, this suppression may lead to reduced clearance of toxic proteins, worsening disease progression.

CD33 in Alzheimer's Disease (AD)

CD33 has been identified as a genetic risk factor for AD. Variants of CD33 can either increase or decrease the risk of developing the disease:

a. Risk Variant (Higher AD Risk): Some CD33 variants lead to higher expression of the receptor, which reduces microglial clearance of β-amyloid. This allows Aβ plaques to accumulate, contributing to synaptic dysfunction and neurodegeneration. Increased CD33 activity also suppresses beneficial microglial responses, worsening brain inflammation.

b. Protective Variant (Lower AD Risk): A protective variant of CD33 results in a less functional receptor, leading to enhanced microglial clearance of Aβ plaques. This helps reduce amyloid burden and lowers AD risk.



[7] *fig no. 3 Intensity of phagocytosis.*

5. TREM2 (Triggering Receptor Expressed on Myeloid Cells 2)

TREM2 is a transmembrane glycoprotein that plays a crucial role in the immune system, particularly in the regulation of microglial function in the brain.

TREM2 is located on chromosome 6p21.1 in humans.

It regulates microglial function, including Phagocytosis (clearing dead cells, debris, and amyloid plaques), Inflammatory response modulation, Lipid metabolism, Cell survival and proliferation.

In Alzheimer's Disease, TREM2's function becomes dysregulated, leading to impaired microglial responses. Some key changes include:

Altered Microglial Response → Microglia with defective TREM2 fail to clear amyloid-beta (Aβ) plaques effectively, leading to plaque accumulation.

Dysfunctional Phagocytosis → Reduced ability to clear toxic proteins and cellular debris.

Increased Inflammation → Instead of regulating inflammation, TREM2-deficient microglia may contribute to chronic neuroinflammation, worsening neuronal damage.Energy and Lipid Dysregulation → TREM2 mutations impair microglial metabolism, reducing their ability to survive and function properly in AD. [8]

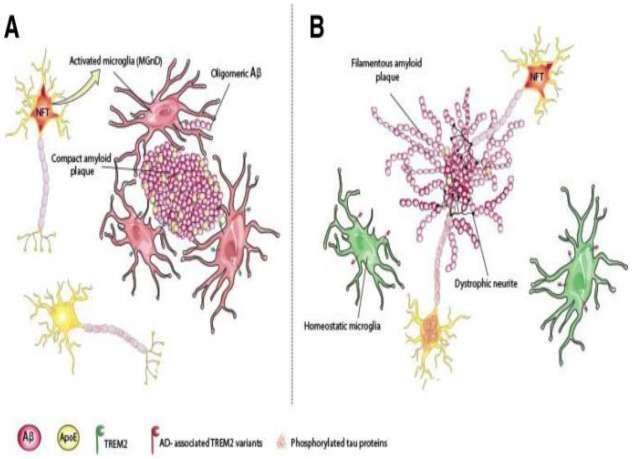


Fig no. 4 Role of TREM2 and its variant in early stage and late stage of Alzheimer's

Proteins involved in Alzheimer's disease

1.Tau protein

1) Tau protein is a microtubule associated protein found in neurons.

2) It plays major role in stabilizing microtubules in neuronal cells which is important for maintaining the structure of the neurons and facilitate intracellular transport.

3) Tau protein is encoded by the gene called MAPT (microtubule-asscociated protein tau) which is located on 17 chromosome.

Role of Tau Protein in Neurons

Tau is a multifunctional protein. The most important function of Tau is in tubulin polymerization in simple words tau binds and stabilizes the microtubule.

On tubulin, the tau interacting site is located at the *C*-terminal end, which is highly acidic. Binding of tau to tubulin is regulated by post-translational modifications, especially by phosphorylation.

In pathological conditions tau self-polymerization and aggregation might also effect the tau -tubulin binding.

Tau dysfunction:

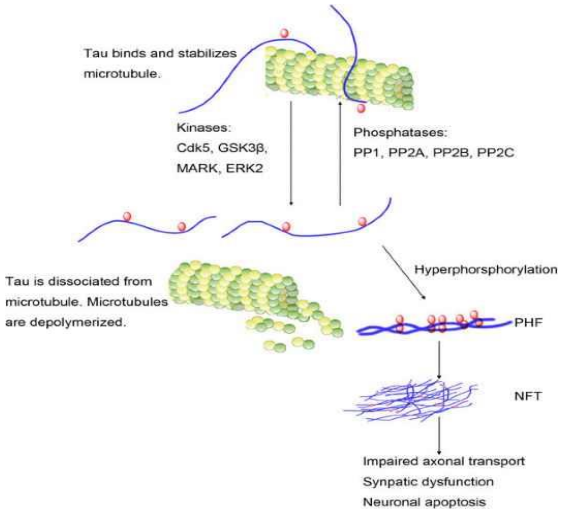


Fig no. 5 Role of Tau protein in Alzheimer's disease

In the pathological condition the tau protein misfolding takes place by abnormal phosphorylated tau which leading to microtubule disintegration.

At such condition tau fails to bind to tublin and form paired helical filaments and gets deposited as tangles. This ultimately leads to intraneuronal signalling pathway. Physiologically tau protein can bind and thereby stabilize microtubules (MTs).

The attachment of tau to MT is regulated by its phosphorylation level. Phosphorylation of tau mediated by kinase (Cdk5, GSK3β, MARK and ERK2) may lead to the detachment of tau from Microtubule and thus, cause MicroTubule depolymerization.

In contrast, phosphatase (PP1, PP2A, PP2B and PP2C) will reduce the phosphorylation level of tau and restore the binding ability of tau for MT. Such equilibrium between the roles of kinases and phosphatases gets disrupted under pathological condition, and increase in the kinase activity and decrease in the phosphatase activity will cause tau hyperphosphorylation.

Hyperphosphorylated tau protein is misfolded and form structure paired helical filaments (PHFs). These structure transitions will lead to more organized aggregates, and thus, eventually develop neurofibrillary tangles (NFT) inside neurons. [9]

2. Apolipoprotein E (ApoE)

Apolipoprotein E is a major cholesterol carrier that supports lipid transport. It has three major isoforms (apoE2, apoE3, and apoE4) with different effects on lipid and neuronal homeostasis. The ε4 allele are at increased risk of AD compared with other alleles

Presence of the *APOE* ε4 allele is also associated with increased risk for cerebral amyloid angiopathy and age-related cognitive decline during normal ageing.

ApoE isoforms differentially regulate Aβ aggregation and clearance in the brain, and have distinct functions in regulating brain lipid transport, glucose metabolism, neuronal signalling, neuroinflammation, and mitochondrial function.

ApoE has an important role in Aβ metabolism. *APOE* genotypes frimly, affect deposition of Aβ to form senile plaques and cause cerebral amyloid angiopathy (CAA), two major hallmarks of amyloid pathology in AD brain.

APOE and Aβ deposition

The main Aβ clearance pathways include receptor-mediated uptake by neurons and microglia, drainage into interstitial fluid or through the BBB, and proteolytic degradation by IDE and neprilysin.

Impaired clearance of Aβ can cause Aβ depasition in brain parenchyma, leading to formation of neurotoxic Aβ oligomers and eventually form amyloid plaques.

Aβ accumulation in the perivascular region leads to CAA, which disrupts blood vessel function. ApoE is primarily synthesized by astrocytes and microglia, and is lipidated by the ABCA1 transporter to form lipoprotein particles.

Lipidated ApoE binds to soluble Aβ and facilitates Aβ uptake through cell surface receptors, including LRP1, LDLR, and HSPG in a manner that probably depends on ApoE isoform and its level of lipidation.

ApoE facilitates binding and internalization of soluble Aβ by glial cells, disrupts Aβ clearance at the BBB. [10]

Classification of drugs used in Alzheimer's disease

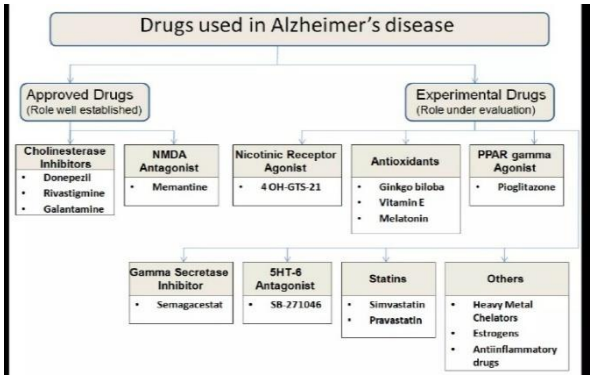


Fig no. 7 Classification of Alzheimer's drugs

APPROVED DRUGS

CHOLINESTERASE INHIBITORS

Eg: Donepezil, Rivastigmine, Galantamine.

The deficiency in cholinergic neurotransmission in Alzheimer's disease has led to the development of

cholinesterase inhibitors as the first-line treatment for symptoms of Alzheimer's disease.

Mechanism of Action

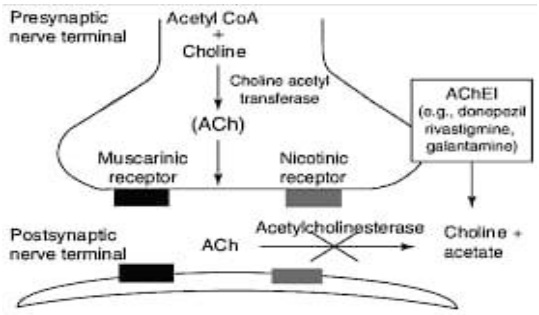


Fig no. 8 Mechanism of action of Acetyl choline in Alzheimer's disease

Cholinesterase inhibitors work by blocking the action of acetylcholinesterase, the enzyme that breaks down acetylcholine into acetate and choline. This inhibition of cholinesterase results in a prolonged presence of acetylcholine in the synaptic cleft (the gap between neurons), allowing it to continue to stimulate the post-synaptic receptors. [11]

NMDA(N-methyl-D-Aspartate) Antagonist

Eg; Memantine

1.N-methyl-D-aspartate (NMDA)antagonist Memantine blocks NMDA receptors slowing down intracellular calcium accumulation.

2.Memantine can be combined with cholinesterase inhibitors such as donepezil, rivastigmine, galantamine especially in individuals with moderate to severe AD. [12]

Mechanism of Action

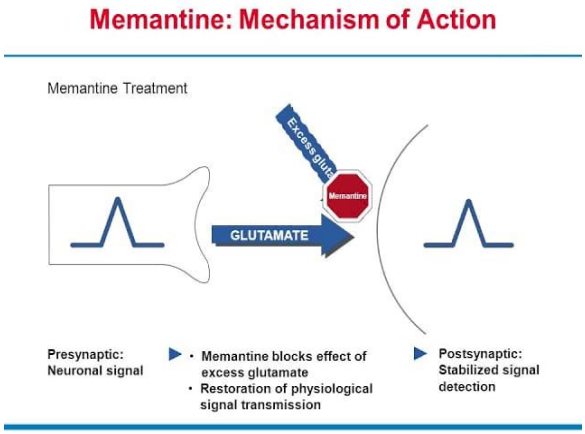


Fig no.9 MOA of Memantine

BACE1 inhibitors

BACE1 is the first enzyme involved in the cleavage of APP, and this cleavage is crucial for the formation of Aβ peptides. These Aβ peptides can aggregate and form plaques, which are believed to contribute to neurodegeneration and cognitive decline in Alzheimer's.

BACE1 inhibitors aim to block this first cleavage step, reducing the production of Aβ peptides.

By inhibiting BACE1, the formation of these toxic Aβ plaques is decreased, which in theory can slow or halt the progression of Alzheimer's disease.

Some BACE1 inhibitors also help to prevent Aβ oligomerization, which is a key step in plaque formation, potentially alleviating the harmful effects on neurons. [13]

NEW DRUGS

LECANEMAB

Lecanemab is a monoclonal antibody used for the treatment of Alzheimer's disease (AD). Its mechanism of action (MOA) targets amyloid-beta (Aβ) plaques, a key pathological feature of Alzheimer's.

Mechanism of Action (MOA)

Selective Binding to Soluble Aβ Protofibrils: Lecanemab specifically targets and binds to soluble

Aβ protofibrils, which are intermediate aggregates between monomers and plaques.

Protofibrils are considered highly neurotoxic and contribute to synaptic dysfunction and neuronal damage.

Reduction of Aβ Plaques: After binding to protofibrils, Lecanemab promotes phagocytosis by microglia, leading to the clearance of Aβ aggregates.

Over time, this results in a reduction of both soluble and insoluble amyloid plaques in the brain.

DONANEMAB

Donanemab(kisunla) is an anti-amyloid monoclonal antibody for the treatment of Alzheimer's disease (AD). It targets amyloid-beta (Aβ) plaques, a hallmark of AD pathology, to slow disease progression.

By binds to amyilod-Beta, reduces the clumps of amyloid-beta and slows he progression of disease.

RI-AG03

RI-AG03 is a peptide-based drug that may help to prevent the buildup of toxic tau proteins in the brain. This buildup is a key driver of neurodegeneration and Alzheimer's disease.

RI-AG03 is the first drug to target both of the two main "hotspots" on the tau protein that cause fibril clumping. It is a promising disease-modifying candidate that may reduce pathogenic tau aggregation in Alzheimer's disease. [14]

CONCLUSION

Genomics and proteomics play a pivotal role in understanding Alzheimer's disease. The key genes like APP, APOE, TREM2, CLU, CD33, PSEN1 & 2 and proteins like Aβ and Tau molecular pathways are responsible for pathological conditions in Alzheimer's disease. There is a lot of scope to study these molecular pathways which helps to identify the new targets for drug discovery and drug development for the better treatment of Alzheimer's disease.

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