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Advances in the pathogenesis of Alzheimer's disease: A re-evaluation of the Amyloid cascade hypothesis

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Abstract

Alzheimer's disease (AD), the most common cause of dementia in the elderly is a common neurodegenerative disease characterized clinically by progressive memory deterioration. The disease becomes clinically obvious as an insidious higher intellectual function impairment with altered mood and behavior, dramatic personality changes, disorientation, declining physical coordination and inability to care for themselves. Histopathological changes including extracellular deposits of amyloid-beta (A-beta) peptides forming senile plaques (SP) and intracellular neurofibrillary tangles (NFT) of hyperphosphorylated tau in the brain. During final stages, victims are bedridden, urinary and bowel function controls may be lost with epileptic attacks. Death is usually due to pneumonia, bedsores or secondary urinary tract infections. These manifestations may indicate severe cortical dis-function. In 5-10 year time, affected individual becomes profoundly disabled, mute and immobile. Death may ensue within an average of 8 years of diagnosis, the last 3 of which are typically spent in institutions. AD is the number one cause of institutionalization in United States of America. An appraisal of the advances in pathogenesis of Alzheimer's disease will be helpful in updating our knowledge on possible etiologies and desired advancements in therapies, clinical care and entire management. Secondly, with the rising cases of AD in tropical regions of the world and coupled with the significant scarcity of literature on Alzheimer's Disease, the need for this compendium becomes obviously necessary, hence we chose to write. This very review derives from focused overview of pathophysiologies and management of AD. Literature searches were sourced from PubMed, Science Direct, Scopus and Google Scholar.

Keywords: Alzheimer's disease; Amyloid-beta (A-beta) peptides; Cortical dis-function; Hyperphosphorylated tau; Intracellular neurofibrillary tangles (NFT); Senile plaques (SP)

1. Introduction

1.1. Alzheimer's disease molecucular pathophysiology

Alzheimer's disease (AD) concedes as progressive neurodegenerative disorder, the foremost cause of dementia in late adult life. It is said to consist of intracellular neurofibrillary tangles (NFTs) and extracellular amyloidal protein deposits as the senile plaques characterize it pathologically. Accumulations of amyloid beta (Aβ) are amyloid plaques in the brain

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parenchymal substance and in the cerebral blood vessels where it is known as congophilic angiopathy also known as cerebral amyloid angiopathy (CAA). These NFTs formed the paired helical filaments with hyperphosphorylated tau proteins and are characterized by the neuronal and synaptic loss and some certain distinctive lesions. Various treatment options are available for this disease process. These may include acetylcholinesterase inhibitors (rivastigmine, galantamine, donepezil) and N-methyl D-aspartate receptor antagonist (memantine) (Thakur et al, 2018). Alzheimer's disease (AD) was originally described by Alois Alzheimer in 1906 and was renamed several years later by Emil Kraepelin (Möller and Graeber 1998, Suzhen et al 2012). It is estimated that over 5 million people live with Alzheimer's disease (AD) in the USA, and it is predicted that by the year 2025 there will be an average 50% increase in patients living with AD (Hebert, et al 2004). Alzheimer's disease (AD) is a common neurodegenerative disease characterized clinically by progressive deterioration of memory, and pathologically by histopathological changes including extracellular deposits of amyloid-beta (A-beta) peptides forming senile plaques (SP) and the intracellular neurofibrillary tangles (NFT) of hyperphosphorylated tau in the brain (Suzhen et al 2012).Alzheimer's disease (AD) was described as "Presenile Dementia" first in 1906 by a German psychiatrist, Alois Alzheimer a colleague of Emil Kraepelin (Omar, et al 2013). In 1901, Alzheimer observed a patient with a progressive loss of cognitive functions (comprehension and memory, unpredictable behaviour etc). Auguste D, the patient died in April 1906 (Maurer, et al 1997, Omar, et al 2013). Alzheimer carried out a postmortem analysis of her brain using histological methods and wrote in the description "Numerous small miliary foci are found in the superior layers. They were determined by storage of peculiar materials in the cortex" (Maurer, et al 1997).

Alzheimer continued: "all in all we have to face a peculiar disease process. Such peculiar disease processes, which have been verified recently in considerable numbers". "Miliar foci, which are characterized by the deposition of peculiar substances in the cortex" are recognized today as senile plaques and "very peculiar changes in the neurofibrils" are recognized today as helical tangles. Emil Kraepelin introduced the eponym "Alzheimer's disease" for "presenile dementia" (Maurer, et al 1997, Omar, et al 2013). More than 100 years after describing Alzheimer's disease, two major pathological processes (amyloid beta and tau protein deposition) observed already by Alois Alzheimer remain the main explanation of pathogenesis of Alzheimer's disease even though some other very important molecular, genetic and epidemiological hypotheses were expressed (Povova, et al 2012). The above notwithstanding, the pathophysiology of Alzheimer's disease has been credited to a number of other factors, though not limited to cholinergic dysfunction, amyloid/tau toxicity and oxidative stress/mitochondrial dysfunction. Apart from the various therapeutic targets, biomarkers and pharmaco-therapies available include; Herbal drugs, secondary metabolites and to some extent non-pharmacological therapies which are impending and potential candidates for the management of AD. The therapeutic options of these Herbal drugs, secondary metabolites and non-pharmacological therapies for the management of AD require further studies for the elucidation of their detailed and elaborate mechanisms (Thakur et al, 2018).

The neurodegenerative process in AD is initially characterized by synaptic damage accompanied by neuronal loss. Recent evidence suggests that alterations in adult neurogenesis in the hippocampus might play a role. Synaptic loss is one of the strongest correlates to the cognitive impairment in patients with AD. Investigations support the notion that the synaptic pathology and defective neurogenesis in AD are related to progressive accumulation of Aβ oligomers rather than fibrils (Leslie and Eliezer, 2010). Hypothesis considered to be the most important in AD are the amyloid metabolic cascade and the posttranslational modification of tau protein, although none of them or other theories alone is sufficient to explain the diversity of biochemical and pathological abnormalities of AD, which is believed to involve a multitude of cellular and biochemical changes (Bachman, et al 1993).

The factors that cause some individuals to depart from the relatively benign process of normal brain aging and instead undergo the pathological cascade that leads to AD are unknown. A number of genetic risk factors for AD have been proposed (Warging and Rosenberg, 2008; Bertram and Tanzi 2008; Harold, et al 2009; Lambert, et al 2009). However, only the apolipoprotein E (APOE) e4-allele, which lowers the age of onset and accelerates the cognitive decline, has a large effect (Kleiman, et al 2006; Stone, et al 2010, Poddtelezhnikov, et al 2011). From the amyloid cascade hypothesis, accumulation of extracellular senile plaques which are primarily made by deposits of Aβ peptide is thought to be one of the most prominent pathogenetic mechanisms of AD. Although the direct causal link between Aβ and impaired neuronal function and memory is still not very clear, it is undoubted that Aβ plays a critical role in the neuropathology of AD (Hardy & Higgins 1992; Hardy, 2006). It is worthy of note that, Aβ plaques were first proposed by Paul Blocq and George Mannesco when they discovered "circular accumulation in the brains of elderly patients" in 1892. After nearly a 100 years of research, Glenner isolated "beta-amyloid" from the meningeal vessels of Alzheimer cases and partially identified the peptide sequence. The amyloid hypothesis was first proposed by John Hardy and David Allsop in 1991. Aβ is a transmembrane protein that is said to be produced by hydrolysis of the Aβ precursor protein (APP) via the amyloidogenic pathway (Fan et al, 2020).

In this update it is important to identify and focus on the new developments of amyloid cascade hypothesis and their relevance to the recent research advances in the genetics, neuropathology and pathogenesis of AD. It is also important to discuss all other possible mechanisms of Alzheimer's disease since it is generally agreed that no single pathogenic mechanism can effectively explain the AD pathology and give a total clue to clinical management and therapies. In the later sections, the recent progress of the studies on genes (see Figure 1) identified to be involved in the production, deposition and degradation of Aβ, the possible contributions of different Aβ assemblies to AD, and their pathological functions will be reviewed (Suzhen, et al 2012). Alzheimer's disease (AD) has been quoted to be the sixth-leading reason of fatality and is 70% present in virtually all cases of dementia. The global burden of AD is expected to accelerate from the current 26.6 million cases in 2006 to 106.8 million by 2050. The total assumed worldwide costs of dementia were US$ 604 billion in 2010, equivalent to 1% of the world's Gross domestic product (GDP) (Thakur et al, 2018).

Figure 1. Aβ and Aβ-related genes in AD. Aβ is a product of sequential cleavage of APP by β-secretase (BACE1) and γ-secretase. γ- Secretase is a multi-protein complex, of which PS1 or PS2 is the catalytic core. After being produced, Aβ is secreted outside the cell and binds to various isoforms of ApoE. These Aβ-binding ApoE isoforms will allow Aβ to undergo metabolism in different pathways, e.g., clearance via BBB, degradation by Aβ-degradating enzymes (IDE or neprilysin), deposition or trafficking into the cell. The affinity of ApoE4 to Aβ is said to be lower than that of ApoE2 or ApoE3. While ApoE2 and ApoE3 help Aβ to be effectively cleared by transport or degradation mechanisms. ApoE4 mainly induce Aβ to aggregation, implicating it to be a high risk factor for AD. There is a feedback existing in vivo to keep proper Aβ levels. When Aβ is generated, AICD (Amyloid precursor protein peptides / APP intracellular fragments) is released, which is translocated into the nucleus and initiates the transcription of neprilysin. Increased neprilysin protein will degradate Aβ and hereby reduces Aβ to a proper level [As Adapted from (Suzhen, et al 2012)]. Alzheimer's disease (AD) is said to accounts for approximate two-thirds of all dementias with an increasing morbidity and heavy financial burden. Recognizing that disease-modifying interventions have the greatest chance of success, the emphasis has shifted to controlling underlying risk factors such as diabetes mellitus, hypertension, smoking, sleep disturbances , and low educational attainment (Zhou et al 2020).

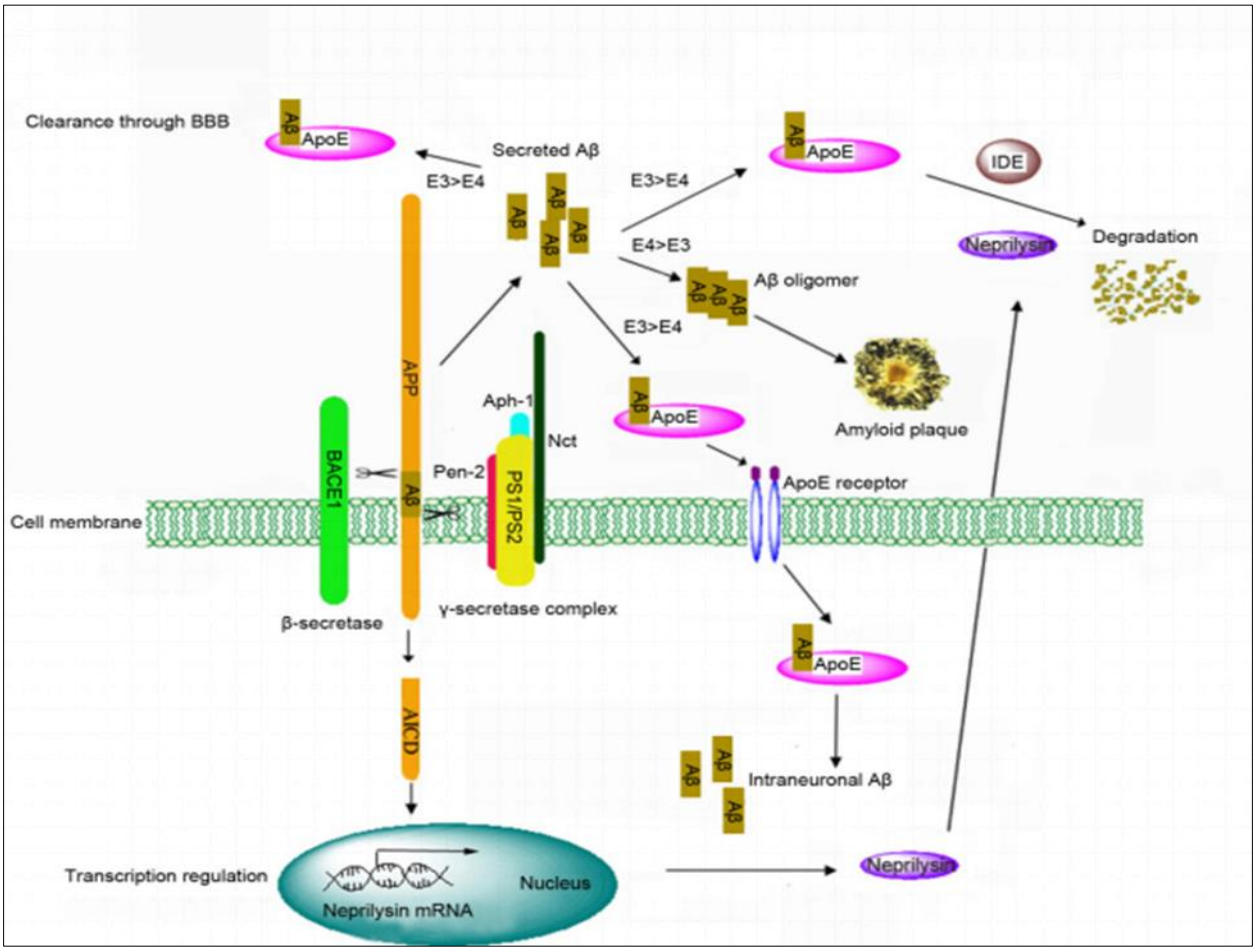

Figure 1 AB AND AB-RELATED GENES IN AD
[Adapted From (Suzhen, et al 2012)].

Another important aspect of Alzheimer's disease pathology has to do with the genetic predisposition to the disease. Alzheimer's disease (AD) can be divided into forms that run in families (genetically inherited) [known as Familial Alzheimer's Disease (FAD)] and forms showing no clear inheritance pattern [known as Sporadic Alzheimer's Disease (SAD)]. FAD accounts for only a small portion (less than 10%) of AD. All FAD are early-onset — usually occurring between ages 30 to 60 — whereas SAD typically occurs after age 65 (Heijmans, 2000).

Although plaques and tangles were originally considered the mediators of neurotoxicity in Alzheimer disease, recent research has underscored the roles of soluble amyloid oligomers and tau molecules. New evidence has re- emphasized the important roles of endocytic, autophagic, and lysosomal pathways in Alzheimer disease pathogenesis—including the finding that deficiency or mutations in the gene that encodes presenilin 1 (the most common cause for early-onset familial Alzheimer disease) impairs the maturation of the lysosomal proton pump (Xiaoning Bi, 2010).

This work intends to discuss recent developments in the perspective of Alzheimer disease pathogenesis and potential therapeutic interventions.

Another implicated factor in the pathogenesis of AD is APO lipoproteins (APOs), which are the protein portion of the lipoproteins (LDL, HDL, VLDL, etc) that transport cholesterol. APO lipoprotein constitutes nearly 60% of some HDL and as little as 1% of chylomicrons. Neurotoxicity due to Aß is mediated, at least in part, by the lipid peroxidation product 4-HydroxyNonEnal (HNE). The cysteine residue of APOE3 and (especially) the two cysteine residues of APOE2 protect against HNE neurotoxicity. APOE4 has no cysteine residues and is therefore not very protective against covalent modification of proteins by HNE (Pedersen, 2002).

Also important is the role of Tau Proteins and Neuro Fibrillary Tangles. Proteins associated with neuronal cytoskeletal components such as the microtubules have a strong influence on both the morphology and physiology of neurons. Tau is a microtubule-associated protein that stabilizes neuronal microtubules under normal physiological conditions. However, in certain pathological situations, tau protein may undergo modifications, mainly through phosphorylation, that can result in the generation of aberrant aggregates that are toxic to neurons. This process occurs in a number of neurological disorders collectively known as Tauopathies, the most commonly recognized of which is Alzheimer's disease (Avila, et al 2004).

Some studies have also implicated Metal Toxicity and Free Radicals in the pathogenesis of AD. More than a hundred years ago inoculation of aluminum phosphate into rabbit brain was demonstrated to produce NeuroFibrillary Tangles (NFTs) resembling the NFTs of Alzheimer's disease (AD). Numerous epidemiological studies have indicated a correlation of aluminum in drinking water with the prevalence of AD, whereas studies of aluminum occupational exposure and aluminum in antacids have shown no correlation (Masahiro et al, 2011).

While the association between smoking and risk of dementia, including Alzheimer's disease, still remains unclear early researchers found that nicotine may improves short-term cognitive performance (Elrod, et al 1988) and inhibits amyloid formation (Solomon, et al 1996). This finding suggested that smoking may be protective against dementia and that nicotine may be cognitively enhancing. More recently, this evidence has been questioned and claims made that the known negative effect of smoking on cardiovascular disease means that it is likely to be a risk factor for vascular dementia (Brayne, 2000).

In addition to Aβ plaques and NFTs, neuroinflammation and glial changes are prominent during AD, and epidemiological evidence, for example, indicates that anti-inflammatory drugs may reduce the risk for AD. Neuroinflammation is prominent during AD and microglias have consistently been implicated in brain aging, neuroinflammation, and neurodegeneration (Marlatt, et al, 2014).

Under normal circumstances neurons are non-dividing (post-mitotic) cells. However, neurons that have entered an aberrant cell cycle are frequently found in Alzheimer's disease (AD). Aberrant cell cycle induction may be the primary cause of neuron death in AD, and precede Aß as well as NFT formation. Counts of hippocampal neurons in both AD and mild cognitive impairment patients show that 5-10% of neurons have cell cycle markers, suggesting that cell cycle antigens could be of benefit in early detection of AD, (Yang, 2003).

From the foregoing, it is worthy of note that AD pathogenesis cannot be fully explained by just a single theory. An understanding of this obvious fact may help us in unraveling the myths surrounding AD pathogenesis, as well as comprehend all that is needed in the total management of the patients and also in drug formulation.

2. Molecular and cellular mechanisms involved in Alzheimer disease pathogenesis

2.1. Hallmark Pathologic Features

Plaques composed mainly of extracellular b-amyloid peptides Neurofibrillary tangles containing hyperphosphorylated tau proteins Synaptic degeneration and selective neuronal death in limbic system and neocortex Accumulation of abnormal endosomes, lysosomes, and mitochondria Glia- mediated inflammation.

Genetic Factors Mutations in genes coding for presenilin 1, presenilin 2, and amyloid Precursor protein (eg, amyloid precursor protein locus duplication and Polymorphisms) Amyloid cascade hypothesis Disruption of neuronal function by b-amyloid oligomers Polymorphism in apolipoprotein E gene.

2.2. Brain Aging

Lysosomal dysfunction (Xiaoning Bi, 2010).

Figure 2 Alzheimer's disease workshop 2012: "emerging concepts in Alzheimer's disease research- new Orleans, Louisiana, USA.

Photo Credits: Copyright © 2012 Diane Bovenkamp, Ph.D., permission from Bright Focus Foundation. Front Row (Left to Right): Maï Panchal, Diane Bovenkamp, Paulina Davis, Rebecca Skerrett, Ingrid Heggland, Elizabeth Steuer, Gwyneth Zakaib. Second Row (Left to Right): William Klein, Paul D. Coleman, Bart P.F. Rutten, Jörg B. Schulz, Jochen Walter, Ilse Dewachter, Cynthia A. Lemere, Frank M. LaFerla, Harry Steinbusch, Stacy Haller, Carol A. Colton, Jin-Moo Lee, Joana A. Palha. Third Row (Left to Right): E. Ronald de Kloet, Edward N. Wilson, Jr, Jochen de Vry, Rylan Allemang-Grand, Julie Dela Cruz, Sarah Hescham, Romina Gentier, Julie C. Savage, Michelle Chua, Nellie Byun, Fernanda Marques, Sandro da Mesquita. Fourth Row (Left to Right): Tatiana Cerveira, Jennifer Goldman, Lionel Breuillaud, Xenos Mason, Sepideh Shokouhi and Guy Eakin. Absent: A. Claudio Cuello, Mark P. Mattson and Michael V. Sofroniew. (Rutten and Steinbusch, 2013). ALZHEIMER'S DISEASE WORKSHOP 2012: "EMERGING CONCEPTS IN ALZHEIMER"S DISEASE RESEARCH- NEW ORLEANS, LOUISIANA, USA.

3. Classification of some studied pathophysiologic / molecular mechanisms involved

- The amyloid cascade hypothesis
- Tau protein and neurofibrillary tangles (nfts)
- Lipoprotein and cholesterol
- The genetic determinants of alzheimer's disease
- Glycation, inflammation and immune response
- Metal toxicity & free radicals
- Aberrant cell cycles

- Nicotine and tobaco (cigarette) smoking
- Other factors.

3.1. The amyloid cascade hypothesis.

From the amyloid cascade hypothesis, accumulation of extracellular senile plaques which are primarily made by deposits of Aβ peptide is thought to be one of the most prominent pathogenetic mechanisms of AD. Although the direct causal link between Aβ and impaired neuronal function and memory is still not very clear, it is undoubted that Aβ plays a critical role in the neuropathology of AD (Hardy & Higgins 1992; Hardy, 2006).

The human amyloid precursor protein (APP) was first identified in 1987 by several laboratories. The APP gene was then mapped to chromosome 21. It has been determined that the APP gene contains 19 exons and spans more than 170 kb. APP has several isoforms generated by alternative splicing of exons 1-13, 13a, and 14 18. The predominant transcripts are APP695 (exons 1-6, 9-18, not 13a), APP751 (exons 1-7, 9-18, not 13a), and APP770 (exons 1-18, not 13a) (Sery et al, 2013).

A first sketch of the amyloid cascade of events in AD can be:

Aß formation ⇒ amyloid plaques ⇒ neuron death ⇒ dementia

The first fact to know in creating a second sketch is that the amyloid beta peptide is created by enzyme clipping of the normal neuron membrane protein known as Amyloid Precursor Protein (APP). APP is actually thought to be a natural neuroprotective agent induced by neuronal stress or injury, which reduces Ca2+ concentration and protects neurons from glutamate excitotoxicity. Injections of a 17-peptide subunit of APP have been shown to significantly reduce ischemic damage (Ben Best, nd).

Enzymes can clip APP in ways that do not result in amyloid beta formation. However, two forms of amyloid beta peptide exist, one of which has 40 amino acids and one of which has 42 amino acids. The enzymes that cleave APP are known as secretases. The two enzymes that initially compete to cleave APP are alpha-secretase (α-secretase) and beta-secretase (β-secretase, BACE1). If alpha-secretase cleaves APP there is no formation of Aß. If APP is cleaved by beta-secretase it can then be further cleaved by gamma-secretase (γ-secretase) to form either a 40 amino acid amyloid peptide (Aß40) which is soluble & mostly innocuous — or a 42 amino acid peptide (Aß42) which clumps together to form insoluble amyloid plaques (Lathia, 2008; Ben Best, nd).

3.1.1. Aβ-related genes: Amyloid precursor protein (APP)

APP is an integral membrane glycoprotein expressed in the brain and central nervous system (CNS). It can undergo sequential proteolytic processing by two pathways the: α pathway and the β pathway. In most cases, APP is sequentially cleaved via α pathway by α-secretase and γ-secretase. The α-secretase cleavage of APP is non-amyloidogentic, whereas the β pathway leads to Aβ generation. In the β pathway APP is initially cleaved by β-secretase to release sAPPβ into extracellular space and leave the 99-amino-acids C-terminal fragment (C99) within the membrane. C99 is subsequently processed to 38-43 amino acids by γ-secretase to release Aβ and APP intracellular C-terminal domain (AICD) (Selko, et al 1994).

In the figures below: The 42 amino acid amyloid beta peptide (Aß42) is more hydrophobic & "sticky" (and hence aggregates more readily) than the 40 amino acid amyloid beta peptide (Aß40). Fibrils of Aß42 clump together to form amyloid plaques ("beta"[ß] refers to the "beta sheet" molecular structure of aggregated Aß). Aß40 & Aß42 are formed intracellularly, but exert damaging effects when transported outside of cells. Whereas Aß42 is the most highly concentrated amyloid-beta in neuritic plaques, Aß40 is more concentrated in cerebrovascular plaques (Lue, 1999).

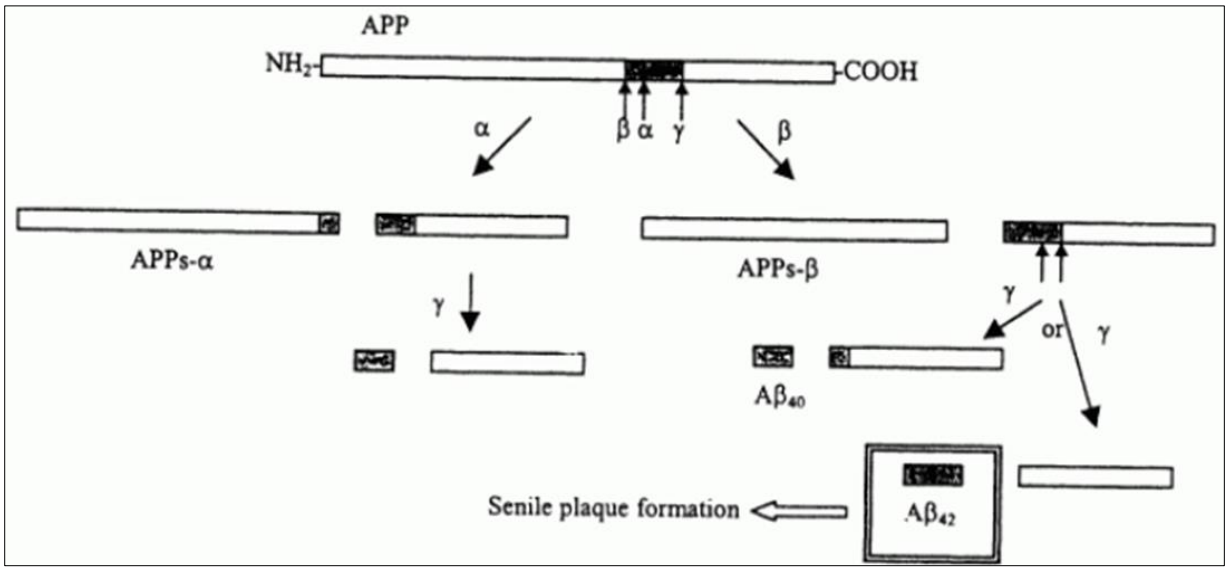

Figure 3 Action of Secretase

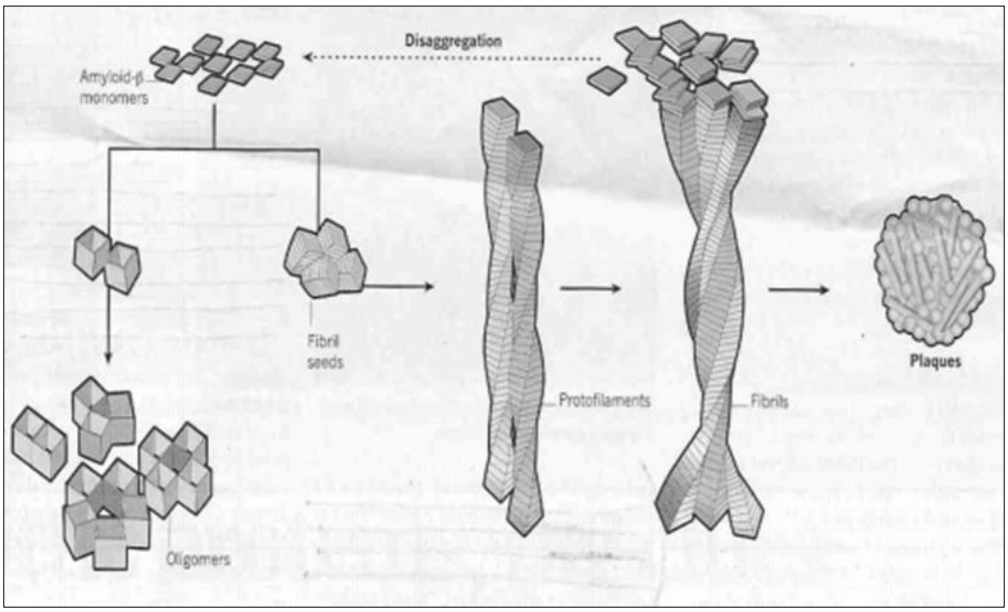

Figure 4 Aß$_{42}$ aggregation

Insulin accelerates transport of intracellular Aß to the extracellular space, which may be one reason why type-2 diabetics have a greatly increased incidence of AD (Gasparini, 2001).

In most cases, the γ-cleavage produces Aβ40, while it could also generate a more toxic variant, Aβ42. It has been recently found that γ-secretase activity for Aβ production could also be negatively regulated by α-secretase, indicating a cross-talk between the pathway and the β pathway (Tina, et al 2010).

Alpha-secretase cleavage occurs at the cell surface, whereas beta-secretase acts at the endoplasmic reticulum. Gamma-secretase produces Aß42 if cleavage occurs in the endoplasmic reticulum and Aß40 if the cleavage is in the trans-Golgi network. Gamma-secretase enzyme not only produces Aß, but some essential proteins, such as Notch (Lathia, 2008).

3.1.2. α -secretase

Amyloid precursor protein (APP) processing by α-secretase precludes the production of small peptides called β-amyloid. APP delivered to the plasma membrane by the cytoskeletal system is subjected to proteolytic processing by α-secretase. A soluble molecule named sAPPα is released after this cleavage. sAPPα has an important role in neuronal

plasticity/ survival and it is protective against excitotoxicity. sAPPα also regulates neural stem cell proliferation and is important for early CNS development (Ohsawa, et al 1999, Sery, et al 2013) .

α-secretase is a zinc metalloproteinase that is also type-I transmembrane protein. The family of proteins with α-secretase activity includes ADAM9, ADAM10 and ADAM17. Constitutive α-secretase is ADAM10 (Kuhn, et al 2010).

Disruption of ADAM10 activity has been shown to decrease the level of soluble non-amyloidogenic APP, suggesting that maintaining ADAM10 activity may play a protective role in Alzheimer's disease for processing of APP via the α-secretase pathway. Biologically important substrates of ADAM10 include the epidermal growth factor (EGF), betacellulin, Notch, and amyloid precursor protein (APP) (Moss, et al 2007).

3.1.3. β -secretase

Absence of the α-secretase cleavage leads to APP molecules internalization into endocytic compartments where they are subjected to cleavage by β- and γ-secretases to generate Aβ. Amyloid precursor protein β-secretase 1 (BACE1) was identified and described (Vassar, et al 1999; Yan, et al 1999, Sery, et al 2013).

β-secretase 1 is β-secretase involved in APP metabolism. β-secretase 1 is a membrane-bound as - partyl protease with a characteristic type I transmembrane domain near C-terminus. The BACE gene is located on chromosome 11 and consists of nine exons coding for a protein of 501 amino acids (Stockley, et al 2008).

β-secretase 1 is still recognized as the drug target for the treatment of Alzheimer's disease even though many important proteins are additional BACE1 substrates, e.g. low/density lipoprotein receptor/related protein, P/selectin glycoprotein ligand/1, neuregulin (Nrg1-type III β1, and Nrg3) and the β2 subunit of voltage- gated sodium channel (Nav1, β2), some of which play an important role in the development and normal function of the brain (Evin, et al 2010).

3.1.4. γ-secretase

αCFT is processed by γ-secretase to p83 peptide that is rapidly degraded and its function was not described. βCFT is cleaved by γ-secretase to Aβ40 and Aβ42. Recently, other sites cleavage by γ-secretase have been described – ζ-site (Aβ46) and ε-site (Aβ49). αCFT is then processed sequentially in ε-site, ζ-site and finally in γ-site (Zhao, et al 2005).

γ-secretase is a big complex composed from a few components, mainly from four proteins: presenilin (PS, PS1 or PS2), nicastrin, anterior pharynx-defective-1 (APH-1) and presenilin enhancer-2 (PEN-2). γ- secretase complex is located in endoplasmic reticulum, Golgi complex and trans-Golgi network, endocytic and intermediate compartments (Spasic, 2007).

3.1.5. Aβ and synaptic dysfunction

Aβ also plays an important role in activity-dependent presynaptic vesicle release (Abramov, et al 2009). Moreover, Aβ can induce neuronal network dysfunction including abnormal induction of excitatory neuronal activity and compensatory inhibitory circuits (Palop, et al 2007). The abnormalities of synapse and neuronal network resulting from Aβ might be the physiological basis of cognitive decline in AD animal models and patients (Suzhen, et al 2012).

Accumulation of cerebral amyloid-beta peptide (Abeta) is said to be essential for development of synaptic and cognitive deficits in Alzheimer's disease. Unfortunately, the physiological functions of Abeta, as well as the primary mechanisms that initiate early Abeta-mediated synaptic dysfunctions, remain largely unknown. Studies on the rodent hippocampal cultures and slices demonstrated increasing extracellular Abeta by inhibiting its degradation enhanced release probability, boosting ongoing activity in the hippocampal network. Presynaptic enhancement mediated by Abeta was found to depend on the history of synaptic activation, with lower impact at higher firing rates. Notably, both elevation and reduction in Abeta levels attenuated short-term synaptic facilitation during bursts in excitatory synaptic connections. These observations suggest that endogenous Abeta peptides have a crucial role in activity-dependent regulation of synaptic vesicle release and might point to a primary pathological events that may lead to compensatory synapse loss in Alzheimer's disease (Abramov, et al 2009).

Important molecular interactions leading to AD neuropathology has been described in amyloid cascade. Since no clinical trials with novel therapies based on amyloid cascade and tau protein hypotheses (see later) have been successful, the main aim of recent AD researches has been focused on the question: what are the primary mechanisms leading to the molecular development of the AD pathology? Promising explanation of triggering mechanism can be seen in vascular pathology that have direct influence on the development of pathological processes typical for Alzheimer disease. Novel

insight into a number of cellular signaling mechanisms, as well as mitochondrial function in Alzheimer disease could also bring explanations of initial processes leading to the development of this pathology. Other studied mechanisms have been outlined in the following sections.

3.2. Tau protein and neurofibrillary tangles (nfts)

Tau is a microtubule-associated protein that stabilizes neuronal microtubules under normal physiological conditions. However, in certain pathological situations, tau protein may undergo modifications, mainly through phosphorylation, that can result in the generation of aberrant aggregates that are toxic to neurons. This process occurs in a number of neurological disorders collectively known as tauopathies, the most commonly recognized of which is Alzheimer's disease (Avilla, et al 2004).

The scientific development of tau pathology is said to be complex and of a multifactorial process. Hyperphosphorylated tau in AD patients' brains causes configuration changes and the loss of tubulin polymerization capacity resulting in defective microtubule functioning (Jara et al, 2018; Fan et al, 2020).

It has been suggested that specific proteins may serve to stabilize microtubules and such proteins including the microtubule-associated proteins (or MAPs) MAP1A, MAP1B, MAP2, and tau (Fig. 1B). In support of this hypothesis, an asymmetric distribution of MAPs (Matus, 1988; Avila et al 2004).

3.2.1. The tau gene

A cDNA for tau was first isolated from a mouse brain expression library, and subsequently, it was cloned from other species including goat, chicken, bovine (133), and human (91, 93, 94). More recently, tau sequences have been described in a number of distinct species (Lee, et al 1988; Himmler, et al 1989; Goedert, et al, 1992; Yoshida and Goedert, 2002; Avila et al 2004).

This tau gene is said to encodes the microtubule-associated protein tau (MAPT) whose transcript undergoes complex, regulated alternative splicing, giving rise to several messenger RNA (mRNA) species. MAPT transcripts are differentially expressed in the nervous system, depending on stage of neuronal maturation and neuron type. MAPT gene mutations have been associated with several neurodegenerative disorders such as Alzheimer's disease, Pick's disease, frontotemporal dementia, cortico-basal degeneration and progressive supranuclear palsy (Gene ID: 4137, updated on 23-Aug-2020).

Human Tau Gene Polymorphism

Two different tau gene haplotypes have been identified (H1 and H2), consisting of eight common single nucleotide polymorphisms. H1 is the most common, and it is over expressed in disorders like Progressive Supranuclear Palsy (PSP) and Corticobasal Degeneration (CBD). In addition, a polymorphic dinucleotide repeat has been also identified in intron 9 (Baker, et al, 1999; Houlden, et al 2001; Pastor, et al 2002; Avila, et al 2004).

Human Tau Gene Expression

The human gene is located on chromosome 17, where it occupies over 100 kb and contains at least 16 exons (10; Fig. 2). Following a GC-rich 5_-region, a single untranslated exon exists (exon-1) (Avila, et al 2004).

Upstream of this exon there are several DNA sequences that contain consensus binding sites for promiscuous transcription factors such as AP2 or SP1. Tau is mainly expressed in neurons, and an interaction with a neural specific factor has been proposed (246, 247). Nevertheless, the neural specific expression of the protein could be also due to the presence of possible silencer elements in nonneural cells (Sadot, et al 1996 a&b; Avila et al, 2004s).

In rare familial AD, the cause of disease is autosomal dominant mutations in Ab precursor protein (APP) or the Ab-producing enzymes presenilins (PSEN1 or PSEN2), which are all thought to lead to increased levels of aggregated Ab (Warging and Rosenberg, 2008; Bertram and Tanzi 2008; Hardy and Selkoe 2002).

Likewise, mutations in tau (MAPT) that predispose it to aggregation can cause specific diseases that involve profound neurodegeneration and dementia (Ballatore et al 2007, Wolfe, 2009; Podtelezhnikov, et al 2011).

Thus, like in other neurodegenerative diseases such as Huntington's disease (HD) and Parkinson's disease, the formation of toxic insoluble aggregates seems to be a key pathogenic step. However, it is not known why these Ab and

tau aggregates accumulate in AD patients nor how they contribute to neuronal dysfunction, particularly for Ab deposits, which can often be found in the brains of elderly non-demented subjects (Schmitt, et al 2000; Podtelezhnikov 2011).

The NFTs first seen by Alzheimer are skeins of twisted abnormal filaments, whose presence in neurons reflects a global disorganization of the neuronal cytoskeleton (Goedert, 1993).

The abnormal filaments, which assume a paired helical structure, hence the name paired helical filaments (PHFs), are composed of tau protein. Although its full repertoire of functions is still unclear, tau is known to bind to microtubules and to stabilize their polymeric structure, thereby facilitating the microtubule's function in axonal transport and structural support (Buee, et al 2000).

Over a half-dozen protein kinases regulate the function of tau, including its affinity for microtubules. The observation that the tau in PHFs is hyperphosphorylated has suggested that altered phosphorylation is important for the development of these lesions (Lovestones et al 1999).

Other modifications of tau, such as proteolysis and glycation, are also considered to be important for PHF formation and for the resistance of PHF to degradation and removal (Grynspan et al 1997).

The importance of tau-related pathology to AD pathogenesis is strongly suggested by the identification of tau mutations in 20% of patients with frontotemporal dementia and in nearly half the patients with frontotemporal dementia who have an affected first-degree relative. In addition, other dementing disorders previously linked to chromosome 17 and characterized by NFT formation in specific neuronal populations are now being found to involve tau mutations or polymorphisms, including progressive supranuclear palsy, corticobasal degeneration, and Pick disease (Buee, et al 2000).

PHF coexists in tangles together with fragments of various cytoskeletal proteins. Notably, abnormally phosphorylated neurofilaments may accumulate as the earliest cytoskeletal alteration associated with dystrophic neurite formation (Dickson, et al 1999).

The distribution and amount of neurofibrillary tangles are correlated with the severity of cognitive impairment in patients with Alzheimer disease (Xiaoning Bi, 2010).

Pathologically AD is characterized by the presence of two insoluble protein aggregates, senile plaques formed from the peptide b-amyloid (Ab) and neurofibrillary tangles composed of hyperphosphorylated tau protein (Goedert and Spillanti 2006; Podtelezhnikov, et al 2011).

Important molecular interactions leading to AD neuropathology has been described in both the Amyloid cascade and the Neurofibrillary tangles as above. Still no clinical trials with novel therapies based on amyloid cascade and tau protein hypotheses have been successful. Novel insight into a number of cellular signaling mechanisms, as well as mitochondrial function in Alzheimer disease could also bring explanations of initial processes leading to the development of this pathology. Other studied mechanisms are as outlined below.

Whole genome expression analysis in a mouse model of tauopathy that expressed human mapt In this whole genome (gene) expression in a genomic mouse model of tauopathy that expressed human MAPT gene under the control of endogenous human MAPT promoter and also were complete knockout for endogenous mouse tau [referred to as 'hTauMaptKO(Duke)' mice]. First, whole genome expression analysis revealed 64 genes, which were differentially expressed (32 up-regulated and 32 down-regulated) in the hippocampus of 6-month-old hTauMaptKO(Duke) mice compared to age-matched non-transgenic controls. Genes relevant to neuronal function or neurological disease include up-regulated genes: PKC-alpha (Prkca), MECP2 (Mecp2), STRN4 (Strn4), SLC40a1 (Slc40a1), POLD2 (Pold2), PCSK2 (Pcsk2), and down-regulated genes: KRT12 (Krt12), LASS1 (Cers1), PLAT (Plat), and NRXN1 (Nrxn1). Second, network analysis suggested anatomical structure development, cellular metabolic process, cell death, signal transduction, and stress response were significantly altered biological processes in the hTauMaptKO(Duke) mice as compared to age-matched non-transgenic controls. Further characterization of a sub-group of significantly altered genes revealed elevated phosphorylation of MECP2 (methyl-CpG-binding protein-2), which binds to methylated CpGs and associates with chromatin, in hTauMaptKO(Duke) mice compared to age-matched controls. Third, phoshpho-MECP2 was elevated in autopsy brain samples from human AD compared to healthy controls. Finally, siRNA-mediated knockdown of MECP2 in human tau expressing N2a cells resulted in a significant decrease in total and phosphorylated tau. Together, these results suggest that MECP2 is a potential novel regulator of tau pathology relevant to AD and tauopathies (Maphis et al, 2017).

3.3. Lipoprotein and cholesterol

APO lipoproteins (APOs), which are the protein portion of the lipoproteins (LDL, HDL, VLDL, etc) that transport cholesterol, are also implicated in the pathogenesis of AD. APO lipoprotein constitutes nearly 60% of some HDL and as little as 1% of chylomicrons. Neurotoxicity due to Aß is mediated, at least in part, by the lipid peroxidation product 4-HydroxyNonEnal (HNE). The cysteine residue of APOE3 and (especially) the two cysteine residues of APOE2 protect against HNE neurotoxicity. APOE4 has no cysteine residues and is therefore not very protective against covalent modification of proteins by HNE (Pedersen, 2002).

LDL-c, is synthesized in the blood vessels and degraded in the liver. As a type of lipoprotein particle, it carries cholesterol into the cells of peripheral tissue. LDL-c causes atherosclerotic cardiovascular disease. Lowering LDL-c level has been shown to reduce myocardial infarction and stroke in high-risk populations. However, whether elevated LDL-c level is related to the risk of AD remains unconfirmed. Several studies reported that patients with AD exhibited higher level of LDL-c when compared with normal controls. In contrast, some of the studies detected no significant difference in LDL-c level between AD patients and healthy controls (Zhou et al, 2020)

On the other hand, many epidemiological studies have observed that circulating HDL levels associate with a reduced risk of Alzheimer's disease. Moreover, it is now understood that the functions of HDL may be more informative than levels of HDL cholesterol (HDL-C). Certain animal model studies have demonstrated that HDL protects against memory deficits,cerebral amyloid angiopathy (CAA) and neuroinflammation. In-vitro studies using state-of-the-art 3D models of the human blood–brain barrier (BBB) have confirmed that HDL reduces vascular Aβ accumulation and also attenuates Aβ-induced endothelial inflammation. Although no HDL-based therapeuties have been tested in clinical trials for Alzheimer's disease, several HDL formulations are in advanced phase of clinical trials for coronary artery disease and atherosclerosis. This could be leveraged toward Alzheimer's disease (Emily et al, 2019).

The above group of researchers found that elevated concentration of LDL-c (>121 mg/dl) may be a potential risk factor for AD. This association is strong in patients aged 60–70 years, but vanishes with advancing age (Zhou et al, 2020).

Vasoprotective functions of hdl relevant for alzheimer's disease hdl has been demonstrated to have at least four distinctive functions capable of protecting against AD. HDL CAN suppress the pathological accumulation of Aβ in cerebral vessels. This is known as cerebral amyloid angiopathy (CAA). HDL can suppress vascular inflammation induced by Aβ or pro-inflammatory cytokines and global neuroinflammation in AD. HDL can also stimulates the production of nitric oxide (NO2) from brain endothelial cells. Finally, HDL delays the fibrillization of Aβ. Although it is unlikely that large, spherical HDL can cross the blood–brain barrier, apoA-I can gain access to the brain via the blood–CSF barrier at the choroid plexus. HDL-like particles in the brain are mainly apoE-based. In humans, ApoE is found in three isoforms: apoE2, apoE3, and apoE4. APOε4 is the major genetic risk factor for late-onset AD and apoE4 has several detrimental functions including delaying Aβ transport out of the brain, promoting blood–brain barrier breakdown, and increasing neuroinflammation (Emily et al, 2019).

Like the other apolipoproteins, APO lipoprotein E (APOE) is synthesized in the liver. But APOE is also independently synthesized in brain astrocytes (and, to a lesser extent in brain oligodendrocytes) — and does not cross the blood-brain barrier. APOE plays a significant role in lipid/cholesterol transport by acting as a binding site for LDL (Low-Density Lipoprotein) receptors — allowing for lipids/cholesterol to be assimilated into cells. The human brain has high levels of myelin to facilitate axon conduction speed and information processing. Myelin is produced by oligodendrocytes. The brain contains 25% of the body's membrane cholesterol — and up to 80% of brain cholesterol is in myelin. Cholesterol allows for the tight packing of membranes seen in myelin sheaths. Myelin repair is dependent upon cholesterol production, recycling, and transport, which is in turn dependent upon APOE (Bartzokis, 2011).

APOE mobilization of cholesterol in the Central Nervous System (CNS) is apparently of particular importance for synapse plasticity & repair of damaged neurons (Simon, et al,2003).

APOE is the major lipoprotein for lipid transport in the cerebrospinal fluid and between cells in the brain tissue itself. APOE could serve to remove oxidized lipids (including oxysterols) from the brain. APOE gene expression has been shown to decrease more than 5–fold in the cerebral cortex of mice as they age (Jiang, 2001).

The APOE4 allele is associated with higher plasma cholesterol and an even higher risk of Alzheimer's disease (AD). Aß binds to both copper and cholesterol, fostering the oxidation of cholesterol to compounds that are extremely toxic to neurons (Nelson, 2005).

The APOE2 allele is associated with lower cholesterol levels and lower AD risk. Having one rather than two APOE4 alleles is a risk factor for women, but not for men. A woman with one APOE4 allele has 4 times the AD than risk a woman with no APOE4 allele. A person with two APOE4 alleles has as much as 16 times the AD risk (International Journal of Clinical Practice 2002, Ben Best, nd).

The APOE2 allele binds & removes amyloid-beta more avidly than APOE3, whereas APOE4 apparently does not bind amyloid-beta at all (Simon, et al 2003).

APOE3 inhibits amyloid ß-sheet formation, whereas APOE4 does not (Evans, 1995).

APOE4 stabilizes Aß in the toxic oligomeric form (Cerf, 2011).

APOE2 and APOE3 have been shown to clear Aß from the brain more effectively than APOE4 (Castellano, 2011).

Individuals having both APOE4 alleles have been shown to have a smaller hippocampus. A study of cognitively normal persons aged 50-63 having both APOE4 alleles showed a 25% decline in cerebral metabolic rate over an interval of 2 years (Reiman, 2001).

Lowered cholesterol can not only reduce Aß production (Wolozin, 2001).

But experiments on hippocampal neurons have shown that a 70% reduction in cellular cholesterol was enough to eliminate Aß formation entirely (Simons, 1998).

APOE4 is associated with increased deposition of Aß, but APOE4 has no effect on the rate of neurofibrillary tangle accumulation (Gomez-Isla, 1997).

From the foregoing, it can be seen that a growing body of evidence in mice, 3D in-vitro models and humans supports a protective role for HDL in cerebrovascular resilience. Since some HDL formulations have already been developed and tested in clinical trials for Cerebrovascular diseases (CVD), it means that with attractive safety profiles, they may offer a novel strategy for prevention or treatment of CVD's associated with Alzheimer's disease (Emily et al, 2019). Also from the outcome of of the study by Zhou and collegues, we may resumptively affirm that elevated concentration of LDL-c (>121 mg/dl) is a potential risk factor for AD. This is strongly associated with age and is significant in patients with AD aged 60–70 years, but vanishes with increasing age. The meta-analysis study, may provide a promising strategy for reducing the risk of AD in patients with hyperlipidemia, which may be achieved by regulating LDL-c concentration between 103.9 and 121 mg/dl with statins (Zhou et al, 2020).

3.4. The genetic determinants of Alzheimer's disease

The genetic predisposition to the Alzheimer disease presents another important aspect of its pathology. Alzheimer's disease (AD) can be divided into forms that run in families (genetically inherited) [known as Familial Alzheimer's Disease (FAD)] and forms showing no clear inheritance pattern [known as Sporadic Alzheimer's Disease (SAD)]. FAD accounts for only a small portion (less than 10%) of AD. All FAD are early-onset — usually occurring between ages 30 to 60 — whereas SAD typically occurs after age 65 (Heijmans, 2000).

Due to its long clinical course, AD has become a major public health problem and genetic susceptibility at multiple genes and interactions among them and/or environmental factors likely influence the risk of AD. This has a strong genetic basis with heritability estimates up to 80%. It has been noted that the effect of APOE*4 allele of APOE on survival in AD has been explored in previous studies; however, results have not been conclusive (Xingbin et al,, 2015).

All FADs can be cited as evidence of the amyloid cascade interpretation of AD causation — against the suggestion that NeuroFibrillary Tangles (NFTs), inflammation, or oxidative stress initiate AD (in FAD, at least). The gene that encodes tau-protein is located on chromosome 17 and is not associated with any FAD. In fact, at least half of FAD cases can be accounted for by the PS1 (Pre-Senilin 1) gene located on chromosome 14. PS1 is the predominant enzyme cleaving the gamma-secretase site. PS1 resides within the endoplasmic reticulum/Golgi complex (Ben Best, nd).

To date, genome-wide association studies (GWAS) have identified more than 20 additional susceptibility loci. These includes BIN1, INPP5D, MEF2C, CD2AP, HLA-DRB1/ HLA-DRB5, TREM2,EPHA1,NME8, ZCWPW1, CLU, PTK2B, CELF1, MS4A6A/MS4A4E, PICALM, SORL1, FERMT2, SLC24A4/ RIN3, DSG2, ABCA7, CD33,TRIP4,TP53INP1, IGHV1-67 and CASS4. Besides the AD risk, genetic variations at these loci may also have the potential to affect survival in AD. The

existing hypothesis have been tested by examining the role of known LOAD genes in AD survival. In addition, studies focusing on AD-related phenotypes, like survival in AD, may help to identify additional AD-relevant genes (Ertekin-Taner et al, 2013; Guerreiro et al, 2013; Lambert et al, 2013; Escott-Price et al 2014; Xingbin et al, 2015).

The mutations on chromosome 19 to the APOE gene are more complicated — more accurately described as a "risk factor" for SAD than as an FAD. APOE occurs in three common forms (alleles): APOE2, APOE3 & APOE4 representing in Caucasians 8%, 78% & 14% of total APOE, respectively. Although only 14% of Caucasians have one APOE4 allele and 2% will have two APOE4 alleles, 40% of AD patients will have at least one APOE4 allele. But each person has two copies of chromosome 19, which means there are 6 combinations of the 3 alleles when taken 2 at a time [e2/e2, e2/e3, e2/e4, e3/e3, e3/e4 and e4/e4] (Andrews, 1988).

Moreover, APOE4 is not a risk factor for mortality (implying cardiovascular disease and dementia mortality) for anyone over age 75 (Heigmans, 2000).

In a genome-wide SNP analysis, we identified multiple novel suggestive loci associated with AD survival, including the top hit at P=6.62E-07 (IL19 on chromosome 1) and 6 loci at P<1E-05 (CCDC85C on chromosome 14 NARS2 on chromosome 11, NCKAP5 on chromosome 2, PKNOX2 on chromosome 11, SDR9C7 on chromosome 12, and ALDH4A1 on chromosome 1). Although these loci are not genome-wide significant and wait confirmation in future studies, we believe they provide insight for future studies as many of them may affect survival through their known associations with AD and other diseases (Xingbin et al, 2015).

3.5. Glycation, inflammation and immune response

Microglia and astrocytes contribute to Alzheimer's disease (AD) etiology and may mediate early neuroinflammatory responses. Despite their possible role in disease progression and despite the fact that they can respond to amyloid deposition in model systems, little is known about whether astro- or microglia can undergo proliferation in AD and whether this is related to the clinical symptoms or to local neuropathological changes. Thus, consistent with animal studies, proliferation in the AD hippocampus is due to microglia, occurs in close proximity of plaque pathology, and may contribute to the neuroinflammation common in AD (Michael, et al 2014).

The Receptor for Advanced Glycation End-products (RAGE) may mediate the activation of microglia, potentiating a positive feedback loop of immune/inflammatory activation. During development, RAGE is a cellular receptor for amphoterin, a protein that mediates neurite outgrowth. But RAGE can act as a receptor for both Advanced Glycation End-products (AGEs) and Aß. Activation of RAGEs by Aß and AGEs results in the expression of more RAGEs, a positive feedback-loop that contributes to Aß toxicity (Schmidt, 1999).

Aß interaction with RAGEs on endothelial cells leads to Aß transport across the blood brain barrier (BBB) as well as the expression of pro-inflammatory cytokines in those cells (Deane, 2003).

In addition to Aβ plaques and NFTs, neuroinflammation and glial changes are prominent during AD, and epidemiological evidence, for example, indicates that anti-inflammatory drugs may reduce the risk for AD (Michael, 20014).

Amyloid-beta activation of microglia causes them to produce inflammatory cytokines like InterLeukin-1ß (IL-1ß) & Tumor Necrosis Factor alpha (TNF−α). Amyloid-beta also activates the transcription factor NF−κB which increases cytokine production by neurons as well as by microglia (Kaltschmidt, B 1997 & Akama, KT, 1998).

3.5.1. Aβ and inflammation

Microglia is rapidly recruited around amyloid plaques after its appearance (Meyer-Luehmann, et al 2008). Aβ can trigger the translocation of microglia from bone marrow to the sites around amyloid plaques (Simart, et al 2006). Aβ up-regulates P38 MAPK or p44/42 MAPK signaling, which may lead to microglia activation with release of cytokines including tumor necrosis factor α (TNF-α) and interleukin-1 β [IL1-β] (Fiala, et al 2007). The microglia around plaques maintains the stability of the plaques (Bolmont, et al 2008). Both pharmacological blockade and genetic knock-out of TNF-α or iNOS down-regulate Aβ-induced cognitive dysfunction in AD mouse model, revealing that TNF-α and iNOS are key mediator of Aβ neurotoxicity (Medeiros, et al 2007).

3.6. Metal toxicity & free radicals

Whilst being environmentally abundant, aluminum is not essential for life. On the contrary, aluminum is a widely recognized neurotoxin that inhibits more than 200 biologically important functions and causes various adverse effects

in plants, animals, and humans. The relationship between aluminum exposure and neurodegenerative diseases, including dialysis encephalopathy, amyotrophic lateral sclerosis and Parkinsonism dementia in the Kii Peninsula and Guam, and Alzheimer's disease (AD) has been suggested (Kawahara and Kato-Negishi, 2011).

Aluminum concentration is elevated in NFTs & amyloid plaques, but this may be an effect of AD rather than a cause. Aß42 may induce lipid peroxidation in the absence of metal catalysts (Butterfield, 2002).

Aß42 enhances superoxide production by macrophages (Klegeris, 1997).

Mercury is also elevated in the AD brain. Mercury can bind to tubulin — the primary protein constituent of microtubules — thereby interfering with microtubule assembly. Zinc & selenium may protect against mercury neurotoxicity.

Mercury is as one of the most toxic elements and causes a multitude of health problems and is also said to be about ten times more toxic to neurons than lead. A study determined if mercury could be causing Alzheimer's disease (AD) by cross referencing the effects of mercury with 70 other factors associated with AD. The results gotten incriminated Mercury as culpable. It found that all the factors involved could be attributed to mercury. The major hallmark changes in AD include plaques, beta amyloid protein, neurofibrillary tangles, phosphorylated tau protein, and memory loss—all changes that can be caused by mercury. The major neurotransmitters like acetylcholine, serotonin, dopamine, glutamate, and norepinephrine are inhibited in patients with AD. The same inhibition occurs in mercury toxicity. While enzyme dysfunction in patients with AD include BACE 1, gamma secretase, cyclooxygenase-2, cytochrome-c-oxidase, protein kinases, monoamine oxidase, nitric oxide synthetase, acetyl choline transferase, and caspases, all these dysfunctions can be explained by mercury toxicity. Also the immune and inflammatory responses seen in patients with AD also occur as cells are exposed to mercury (Sibelerud et al, 2019).

Although the role of Aluminium remains controversial, recent research has produced more definitive information about zinc, copper & iron — all of which are enriched in amyloid-beta plaques in AD. All three metals lead to Aß aggregation, but chelation can completely reverse metal-induced precipitation of Aß (Cherny, 2001).

Copper particularly mediates Aß toxicity, whereas zinc inhibits toxicity (Maynard 2002).

Aß is not toxic to neurons in the absence of Cu2+ (Opazo, 2002).

Aß converts Cu2+ and Fe3+ to Cu+ and Fe2+, both of which generate free radicals by the Fenton Reaction (Cuajungco, 2000).

Fe3+ induces aggregation of phosphorylated NFTs, but this aggregation can be reversed by reducing Fe3+ to Fe2+ (Yamamoto, 2002).

Although zinc binds-to and precipitates amyloid-beta, it may have a protective effect by displacing copper & iron enriched in amyloid-beta plaques in AD. On the other hand, there is evidence that zinc can initiate plaque formation by its ability to bind to Aß under non-acidic conditions and by creating the inflammation which leads to acidity. Under acidic conditions — such as exists in inflammed tissue — copper displaces zinc (Brain research reviews, 2003).

In its free state amyloid-beta has antioxidant properties which have beneficial effects for neurons. But amyloid-beta aggregation by acidic conditions and by copper, iron, zinc & aluminum results in the highly toxic & pro-oxidant ß-sheets. The binding is particularly strong for copper. Copper binds more strongly to Aß42 than to Aß40 and copper is a greater catalyst of free radical formation than are the other metals [FREE RADICAL BIOLOGY & MEDICINE 31(9):1120-1121 (2001)]. Cu2+ bound to free Aß42 is reduced by O2 to produce H2O2 (Opazo, 2002).

More toxicities from metals and free radicals have been reported in several journals,

3.7. Aberrant cell cycles

Neurons are normally non-dividing (post-mitotic) cells, but neurons that have entered an aberrant cell cycle are frequently found in Alzheimer's disease (AD). Aberrant cell cycle induction may be the primary cause of neuron death in AD, and precede Aß as well as NFT formation. Counts of hippocampal neurons in both AD and mild cognitive impairment patients show that 5-10% of neurons have cell cycle markers suggesting that cell cycle antigens could be of benefit in early detection of AD (Yang, 2003).

The fact that clearance of Aß from hippocampal tissue by injection of anti-Aß antibody leads to removal of early tau pathology provides strong evidence for the amyloid-cascade hypothesis (LaFerla, 2005).

Aß toxicity is considerably mediated through caspase−12 enzyme in the endoplasmic reticulum (Nakagawa, 2000).

Caspase-cleaved tau protein accelerates the aggregation and filament formation of full-length tau, which co-localizes with Aß, aggravating the tangles (Rissman, 2003).

The fact that the genetic mutations affecting Aß production (PS1, PS2 and APP proteins) are behind Familial Alzheimer's Disease (FAD, inherited AD) has been taken as strong evidence for the Amyloid Cascade Hypothesis. But mutations in these proteins can also be used as evidence for an "Aberrant Cell Cycle Hypothesis" of AD. Overexpression of APP can drive neurons into a cell cycle leading to apoptosis (Chen, 2000).

PS2 overexpression leads to cell cycle arrest preceding apoptosis in cell cultures (Janicki, 1999).

Mice genetically disposed to hyperphosphorylated, aggregated tau will display neurodegeneration associated with abnormal neuronal cell-cycle re-entry leading to cell death (Andorfer, 2005).

Three variants of PS1 mutations lead to a degree of cell cycle inhibition that correspond to the age of onset of FAD in humans afflicted with those mutations (2000).

3.8. Nicotine and tobaco (cigarette) smoking

Several early epidemiological studies claimed that cigarette smoking has a protective effect against Alzheimer's Disease (Neuroepidemiology, 1992). Such studies have been criticized on many methodological grounds. More nicotine receptors and fewer senile plaques are not surprising among autopsies of smokers if they are dying at a younger age than non-smokers.

More recent prospective (cohort) studies found opposite results from the earlier cross-sectional or prevalence studies. A prospective Rotterdam Study found that the incidence of AD is more than double for smokers as compared to non-smokers [smoking was not an additional risk factor for those having the APOE4 allele] (Lancet, 1998).

The Honolulu Heart Program (a longitudinal cohort study) also found more than twice the risk for AD among medium & heavy smokers as compared to non-smokers (Neurobiology, 2003).

Large scale observational studies show nearly twice the risk of AD for smokers, as compared to non-smokers or (to a lesser extent) former smokers (Anstey, 2007).

Nonetheless, a mouse model has shown a worsening of tau protein pathology (NFTs) due to nicotine administration (Oddo, 2005).

Tobacco smoke is a lethal substance, so claims of its possible benefits against AD should be viewed with caution. In a 40-year longitudinal study of tens of thousands of British Physicians, the death rate between the ages of 35 to 69 was only 20% for non-smokers as compared to 41% for smokers as a whole and 50% for those who smoked more than 25 cigarettes per day. Of those who survived to age 70, non-smokers had twice the chance of living to age 85 as smokers (BMJ, 1994).

Even if nicotine is proven decisively to be of benefit in AD, it should be administered as nicotine patches rather than as tobacco smoke — which contains carbon monoxide, cadmium and thousands of other toxins which may contribute to AD. If AD is a vascular disease, the damaging effects of the toxins in tobacco smoke on the vasculature alone could easily outweigh possible increases in brain NGF. And if AD is not a vascular disease, tobacco smoke certainly nonetheless contributes to vascular dementia.

3.9. Other possible mechanisms triggering Alzheimer’s disease pathology.

Vascular and mitochondrial hypotheses of pathogenesis of AD were also stated. Several vascular risk factors e.g. diabetes mellitus, hypertension, atherosclerosis, hypercholesterolemia, metabolic syndrome and obesity, have been found to be associated with Alzheimer’s disease (Pluta, et al 2010a & Pluta, et al 2012b). The apolipoprotein E genotype with the link to dynamics of cholesterol transport is also implicated as a vascular risk factor in influencing AD (Kalaria, et al 2012). Alzheimer’s Disease patients often exhibit various cerebrovascular pathologies including cerebral micro

bleeding (DeReuck, et al 2012; DeReucket al, 2012 & Nakata-Kudo et al, 2012) and cerebral microinfarcts. Microinfarcts are common in patients with vascular dementia (weighted average 62%), Alzheimer's disease (43%), and demented patients with both Alzheimer-type and cerebrovascular pathology (33%) compared with nondemented older individuals (24%) (Brundel, et al 2012). Cerebral hypoperfusion may initiate and/or accelerate the neurodegeneration cascade causing amyloid deposition, synaptic and neural dysfunction and lead to cognitive impairment (Kalaria, et al 2012; Pluta, et al 2010a & Pluta, et al 2012b). Aβ deposition into the capillary wall is strongly associated with the ApoE4 allele as a risk factor (Attems, et al 2010). Oxidative stress that can be influenced by hypoxia and also by mitochondrial dysfunction is associated with AD pathogenesis.

In one of the studies cited above, fifty (50) AD patients were assessed alongside 26 controls to detect latent brain hemorrhages using gradient-echo T(2) weighted images which is a sensitive magnetic resonance imaging technique capable of detecting hemosiderin (iron storing protein) components in the brain. Micro bleeds, demarcated as low-intensity spots in T(2)*-weighted images, were detected in 16.7% of AD patients without cerebrovascular disease (CVD) and in 12.5% of those with CVD, while no micro bleeding was detected in their control counterparts. However, no statistical significant difference was observed between the micro bleed-positive group and the micro bleed-negative group in their clinical background, such as hypertension, the use of antiplatelet drugs and smoking. In addition, white matter high intensities in the T(2)-weighted image were significantly more confluent in the micro bleed-positive AD group than its negative counterpart. The researchers concluded that the AD brains did reveal latent micro bleeds in the Alzheimer's disease patients are more frequent than in normal controls. Micro bleeds not being related to common hemorrhagic risk factors, but being significantly related to white matter pathologies suggested that micro bleeds in AD may be associated with Cerebral amyloid angiopathy (CAA), but not with hypertension or cerebrovascular disease (CVD) (Nakata-Kudo et al, 2012).

3.10. Treatment modalities for Alzheimer's

In view of an increasingly aging society as expected, the number of AD patients and sociomedical burdens will continue to increase. It is currently noted that only the cholinesterase inhibitors (AChEIs) and the NMDA receptor antagonist are the only therapies for AD. Moreover, these agents can only relieve symptoms and not delay the progress of AD pathogenesis (Panza et al, 2917; Fan et al, 2020). While three of the cholinesterase inhibitors, namely, donepezil, rivastigmine, and galantamine, which are approved by the US Food and Drug Administration, were proven to increase side effects, such as nausea, vomiting, and diarrhea, the NMDA receptor antagonist, memantine showed good effects on improving cognitive function and behavioral disturbance scores, it causes severe hypotension, leading to fainting, and falls. According to statistics, AD drug development had a high failure rate of 99.6% in the decade between 2002 and 2012. Researchers are constantly proposing new pathogenic mechanisms based on the unsatisfactory results above (Aoyagi et al, 2019; Egan et al, 2019; Fan et al, 2020).

4. Conclusion

Alzheimer's disease (AD) is the most common cause of dementia, affecting more than 10% of people over the age of 65. Although considerable progress in the understanding of the molecular mechanisms of the pathogenesis of AD has been made, many aspects, especially key mechanisms that release pathologies, remain controversial. Promising research is focused on the research of hypoxia and oxidative stress caused by different mechanisms, e.g. by vascular and mitochondrial pathologies.

Aβ deposition in different cell compartments and in extracellular areas and its pathophysiological role remains to be explained in relationship to other molecular mechanisms. It could be concluded that up to date we know many mechanisms that could affect set up and progress of AD pathogenesis. It seems like AD is not only one or two types of diseases but it could be a group of diseases with similar APP and Tau pathologies that are triggered by different mechanisms. Genetic disposition to AD would play an important role in the mechanisms of Alzheimer's disease initiations.

Alzheimer's Disease pathophysiological processes and treatment researches are expanding rapidly and is far reaching the phase in which findings from fundamental neuroscience can drive the development of effective novel diagnostic and therapeutic strategies with proven capacities, hopefully resulting in useful clinical tools to improve prevention and treatment of this devastating neurodegenerative disorder in the not-too-distant future.

Compliance with ethical standards

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Disclosure of Conflict of interest

In the course of this study, up till this time of publication there has been no conflict of interest.

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References

[1] Abramov E, Dolev I, Fogel H, Ciccotosto GD, Ruff E, Slutsky I. Amyloid-β as a positive endogenous regulator of release probability at hippocampal synapses. Nat Neurosci. 2009; 12: 1567-1576.

[2] Andorfer C. Journal Of Neuroscience. 2005; 25(22): 5446-5454.

[3] Andrews HF. The APOE= Allele and The Risk of AD Among Africans American, Whites & Hispanics. 1988; 279(10): 751-755.

[4] Aoyagi A, Condello C, Stohr J, Yue W, Rivera BM, Lee JC, et al. Aβ and tau prion-like activities decline with longevity in the Alzheimer's disease human brain. Sci Transl Med. 2019; 11: eaat8462.

[5] Akama KT. Proceedings of The National Academy Of Sciences (USA). 1998; 95(10): 5795-5800.

[6] Anstey KJ. American Journal Of Epidemiology. 2007; 166(4): 367-378.

[7] Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT. Neurofibrillary tangles but not senile Plaques parallel duration and severity of Alzheimer disease. Neurology. 1992; 42 (3 pt 1): 631-639.

[8] Attems J, Yamaguchi H, Saido TC, Thal DR. Capillary CAA and perivascular Aβ-deposition: two distinct features of Alzheimer's diseasepathology. J Neurol Sci 2010; 299: 155-162.

[9] Avila J, Lucas JJ, Perez M. Role of Tau Proteins in the Physiological and Pathological Conditions. Physiol Rev. 2004; 84: 361 – 384.

[10] Bachman DL, Wolf PA, Linn RT, Knoefel JE, Cobb JL, Belanger AJ, White LR, D'Agostino RB. Incidence of dementia and probable Alzheimer's disease in a general population: the Framingham Study. Neurology. 1993; 43: 515-519.

[11] Baker M, Litvan I, Houlden H, Adamson J, Dickson D, Perez-Tur J, Hardy J, Lynch T, Bigio E, Hutton M. Association of an extended haplotype in the tau gene with progressive supranuclear palsy. Hum Mol Genet. 1999; 8: 711–715.

[12] Ballatore C, Lee VM, Trojanowski JQ. Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. Nat Rev Neurosci. 2007; 8: 663–672.

[13] Bartzokis G. Neurobiology of Aging. 2007; 32(8):1341-1371.

[14] Ben, B. (nd). www.benbest.com/lifeex/alzheimers.html.

[15] Bertram L, Tanzi, RE. (2008). Thirty years of Alzheimer's disease genetics: the Implications of systematic meta-analyses. Nat Rev Neurosci. 2008; 9: 768–778.

[16] Bolmont T, Haiss F, Eicke D, Radde R, Mathis CA, Klunk WE, Kohsaka S, Jucker M, Calhoun ME. Dynamics of the microglial/amyloid interaction indicate a role in plaque maintenance. J Neurosci. 2008; 28: 4283-4292.

[17] Brain Research Reviews. 2003; 41:44-56.

[18] Brayne C. Smoking and the brain. BM.J 2000; 320: 1087-8.

[19] British Journal Of Medicine. 1994; 309: 901-911.

[20] Brundel M, de Bresser J, van Dillen JJ, Kappelle LJ, Biessels GJ. (2012). Cerebral microinfarcts: a systematic review of neuropathological studies. J Cereb Blood Flow Metab. 2012; 32: 425-436.

[21] Buee M, Rossignol M, Jauneau A. The pre-symbiotic growth of arbuscular mycorrhizal fungi is induced by a branching factor partially purified from plant root exudates. Mol Plant Microbe Interact. 2000; 13: 693–698.

[22] Butterfield DA. Neurobiology Of Aging. 2002; 23(5): 655-664.

[23] Castellano JM. Science Translational Medicine. 2011; 3(89): 1-11.

[24] Cerf E. Faseb Journal. 2011; 25(5): 1585-1595.

[25] Chen Y. Journal Of Biological Chemistry. 2000; 275(12): 8929-8935.

[26] Cherny RA. Neuron. 2001; 30(3): 665-676.

[27] Cuajungco MP. Journal Of Biological Chemistry. 2000; 275(26): 19439-19442.

[28] Dickson TC, King CE, McCormack GH. Neurochemical diversity of dystrophic neurites in the early and late stages of Alzheimer's disease. Exp Neurol. 1999; 156: 100–110.

[29] Deane R. Nature Medicine. 2003; 9(7): 907-913.

[30] De Reuck JL, Deramecourt V, Cordonnier C, Leys D, Pasquier F, Maurage CA. Cerebrovascular lesions in patients with frontotemporal lobar degeneration: a neuropathological study. Neurodegener Dis. 2012; 9: 170-175.

[31] De Reuck JL, Cordonnier C, Deramecourt V, Auger F, Durieux N, Bordet R, Maurage CA, Leys D, Pasquier F. Microbleeds in Postmortem Brains of Patients With Alzheimer Disease: A T2*-weighted Gradient- Echo 7.0 T Magnetic Resonance Imaging Study. Alzheimer Dis Assoc Disord. 2012.

[32] Egan MF, Kost J, Voss T, Mukai Y, Aisen PS, Cummings JL, et al. Randomized trial of verubecestat for prodromal alzheimer's disease. N Engl J Med. 2019; 380: 1408–20.

[33] Elrod K, Buccafusco JJ, Jackson WJ. Nicotine enhances delayed matching-to-sample performance by primates. Life Sci. 1988; 43: 277-87.

[34] Emily BB, Jerome R, Tara CM, Jianjia F, Wenchen Z, Chery WL. HDL from an Alzheimer's disease perspective. Current Opinion in Lipidology. June 2019; 30(3): 224-234.

[35] Ertekin-Taner N, De Jager PL, Yu L, Bennett DA. Alternative Approaches in Gene Discovery and Characterization in Alzheimer's Disease. Curr Genet Med Rep. 2013; 1: 39–51.

[36] Escott-Price V, Bellenguez C, Wang LS, Choi SH, Harold D, Jones L, Holmans P, Gerrish A, Vedernikov A, Richards A, DeStefano AL, Lambert JC, Ibrahim-Verbaas CA, Naj AC, Sims R, Jun G, Bis JC, Beecham GW, Grenier-Boley B, Russo G, Thornton-Wells TA, Denning N, Smith AV, Chouraki V, Thomas C, Ikram MA, Zelenika D, Vardarajan BN, Kamatani Y, Lin CF, Schmidt H, Kunkle B, Dunstan ML, Vronskaya M, Johnson AD, Ruiz A, Bihoreau MT, Reitz C, Pasquier F, Hollingworth P, Hanon O, Fitzpatrick AL, Buxbaum JD, Campion D, Crane PK, Baldwin C, Becker T, Gudnason V, Cruchaga C, Craig D, Amin N, Berr C, Lopez OL, De Jager PL, Deramecourt V, Johnston JA, Evans D, Lovestone S, Letenneur L, Hernandez I, Rubinsztein DC, Eiriksdottir G, Sleegers K, Goate AM, Fievet N, Huentelman MJ, Gill M, Brown K, Kamboh MI, Keller L, Barberger-Gateau P, McGuinness B, Larson EB, Myers AJ, Dufouil C, Todd S, Wallon D, Love S, Rogaeva E, Gallacher J, George-Hyslop PS, Clarimon J, Lleo A, Bayer A, Tsuang DW, Yu L, Tsolaki M, Bossu P, Spalletta G, Proitsi P, Collinge J, Sorbi S, Garcia FS, Fox NC, Hardy J, Naranjo MC, Bosco P, Clarke R, Brayne C, Galimberti D, Scarpini E, Bonuccelli U, Mancuso M, Siciliano G, Moebus S, Mecocci P, Zompo MD, Maier W, Hampel H, Pilotto A, Frank-Garcia A, Panza F, Solfrizzi V, Caffarra P, Nacmias B, Perry W, Mayhaus M, Lannfelt L, Hakonarson H, Pichler S, Carrasquillo MM, Ingelsson M, Beekly D, Alvarez V, Zou F, Valladares O, Younkin SG, Coto E, Hamilton-Nelson KL, Gu W, Razquin C, Pastor P, Mateo I, Owen MJ, Faber KM, Jonsson PV, Combarros O, O'Donovan MC, Cantwell LB, Soininen H, Blacker D, Mead S, Mosley TH, Jr, Bennett DA, Harris TB, Fratiglioni L, Holmes C, de Bruijn RF, Passmore P, Montine TJ, Bettens K, Rotter JI, Brice A, Morgan K, Foroud TM, Kukull WA, Hannequin D, Powell JF, Nalls MA, Ritchie K, Lunetta KL, Kauwe JS, Boerwinkle E, Riemenschneider M, Boada M, Hiltunen M, Martin ER, Schmidt R, Rujescu D, Dartigues JF, Mayeux R, Tzourio C, Hofman A, Nothen MM, Graff C, Psaty BM, Haines JL, Lathrop M, Pericak-Vance MA, Launer LJ, Van Broeckhoven C, Farrer LA, van Duijn CM, Ramirez A, Seshadri S, Schellenberg GD, Amouyel P, Williams J. Gene-wide analysis detects two new susceptibility genes for Alzheimer's disease. PLoS One. 2014; 9: e94661.

[37] Evans KC. Proceedings of the National Academy of Sciences (USA). 1995; 92(3): 763-767.

[38] Evin G, Barakat A, Masters CL. BACE: Therapeutic target and potential biomarker for Alzheimer's disease. Int J Biochem Cell Biol. 2010; 42: 1923-1926.

[39] Fan L, Mao C, Hu X, Zhang S, Yang Z, Hu Z, Sun H, Fan Y, Dong Y, Yang J, Shi C, Xu Y. New Insights Into the Pathogenesis of Alzheimer's Disease. Front. Neurol. 2010; 10: 1312

[40] Fiala M, Cribbs DH, Rosenthal M, Bernard G. Phagocytosis of amyloid-beta and inflammation: two faces of innate immunity in Alzheimer's disease. J Alzheimers Dis. 2007; 11: 457-463

[41] Gasparini L, Gouras GK, Wang R, Gross RS, Flint BM, Greengard P, Hauxi Xu. Stimulation of B-Amyloid Precursor Protein. Traffiking By Insulin Reduces Intraneuronal B-Amyloid and Requires Mitogen-Activated Protein Kinase Signaling. The Journal of Neuroscience. 2001; 21(8): 2561-2570.

[42] Images For Gene ID: 4137, Updated on 23-Aug-2020

[43] Goedert M, Spillantini MG, Cairns NJ, Crowther, RA. Tau proteins of Alzheimer paired helical filaments: abnormal phosphorylation of all six brain isoforms. Neuron. 1992; 8: 159–168.

[44] Goedert M. Tau protein and the neurofibrillary pathology of Alzheimer's disease. Trends Neurosci. 1993; 16: 460–465

[45] Goedert M, Spillantini MG. A century of Alzheimer's disease. Science. 2006; 314: 777–781.

[46] Gomez-Isla T, Hollister R, West H. Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer disease. Ann Neurol. 1997; 41 (1): 17-24.

[47] Gomez-Isla T. ANNALS OF NEUROLOGY. 1997; 41(1): 17-24.

[48] Graham WV, Bonito-Oliva A, Sakmar TP. Update on alzheimer's disease therapy and prevention strategies. Annu Rev Med. 2017; 68: 413–30.

[49] Grynspan, F, Griffin, WR, Cataldo, A. Active site-directed antibodies identify calpain II as an early-appearing and pervasive component of neurofibrillary pathology in Alzheimer's disease. Brain Res. 1997; 763: 145–158.

[50] Guerreiro R, Wojtas A, Bras J, Carrasquillo M, Rogaeva E, Majounie E, Cruchaga C, Sassi C, Kauwe JS, Younkin S, Hazrati L, Collinge J, Pocock J, Lashley T, Williams J, Lambert JC, Amouyel P, Goate A, Rademakers R, Morgan K, Powell J, St George-Hyslop P, Singleton A, Hardy J. TREM2 variants in Alzheimer's disease. N Engl J Med. 2013; 368: 117–127.

[51] Hardy J. Alzheimer's disease: the amyloid cascade hypothesis: an update and reappraisal. J Alzheimers Dis. 2006; 9: 151-153.

[52] Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. Science. 1992; 256: 184-185.

[53] Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. Science. 297: 353–356.

[54] Harold, D, Abraham, R, Hollingworth, P, Sims, R, Gerrish, A. Genome-wide association study identifies variants at CLU and PICALM Associated with Alzheimer's disease. Nat Genet. 2019; 41: 1088–1093.

[55] Heijmans BT. Experimental Gerontology. 2000; 35(6-7): 865-877.

[56] Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. State-specific projections through 2025 of Alzheimer disease prevalence. Neurology. 2004; 62: 1645.

[57] Himmler A. Drechsel D, Kirschner MW, Martin DJ. Tau consists of a set of proteins with repeated C-terminal microtubule binding domains and variable N-terminal domains. Mol Cell Biol. 1989; 9: 1381–1388.

[58] Houlden H, Baker M, Morris HR, MacDonald N, Pickering- Brown S, Adamson J, Lees AJ, Rossor MN, Quinn NP, Kertesz A, Khan MN, Hardy J, Lantos PL, St George-Hyslop P, Munoz DG, Mann D, Lang AE, Bergeron C, Bigio EH, Litvan I, Bhatia KP, Dickson D, Wood NW, Hutton M. Corticobasal degeneration and progressive supranuclear palsy share a common tau haplotype. Neurology. 2001; 56: 1702–1706.

[59] International Journal of Clinical Practice. 2002; 56(3):197-203.

[60] Janicki SM. Neurobiology Of Aging. 2000; 21(6): 829-836.

[61] Janicki SM. American Journal Of Pathology. 1999; 155(1): 135-144.

[62] Jara C, Aranguiz A, Cerpa W, Tapia-Rojas C, Quintanilla RA. Genetic ablation of tau improves mitochondrial function and cognitive abilities in the hippocampus. Redox Biol. 2018; 18: 279–94.

[63] Jiang, CH. Proceedings of The National Academy of Sciences (USA). 2001; 98(4): 1930-1934.

[64] Kalaria RN, Akinyemi R, Ihara M. Does vascular pathology contribute to Alzheimer changes? J Neurol Sci. 2012; 322: 141-147.

[65] Kaltschmidt B. Proceedings Of The National Academy Of Sciences (USA). 1997; 94(6): 2642-2647.

[66] Klegeris A. Journal Of Neuroscience Research. 1997; 49(2): 229-235.

[67] Kleiman T, Zdanys K, Black B, Rightmer T, Grey M. Apolipoprotein E epsilon4 allele is unrelated to cognitive or functional decline in Alzheimer's disease: retrospective and prospective analysis. Dementia Geriatric Cognitive Disord. 2006; 22: 73–82.

[68] Kuhn PH, Wang H, Dislich B, Colombo A, Zeitschel U, Ellwart JW, Kremmer E, Rossner S, Lichtenthaler SF. ADAM10 is the physiologically relevant. 40 constitutive alpha-secretase of the amyloid precursor protein in primary neurons. EMBO J. 2010; 29: 3020-3032.

[69] LaFerla FM. Trend In Molecular Medicine. 2005; 11(4): 171-176.

[70] Lambert JC, Heath S, Even G, Campion D, Sleegers K. Genomewide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nat Genet. 2009; 41: 1094–1099.

[71] Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, Jun G, Destefano AL, Bis JC, Beecham GW, Grenier-Boley B, Russo G, Thornton-Wells TA, Jones N, Smith AV, Chouraki V, Thomas C, Ikram MA, Zelenika D, Vardarajan BN, Kamatani Y, Lin CF, Gerrish A, Schmidt H, Kunkle B, Dunstan ML, Ruiz A, Bihoreau MT, Choi SH, Reitz C, Pasquier F, Hollingworth P, Ramirez A, Hanon O, Fitzpatrick AL, Buxbaum JD, Campion D, Crane PK, Baldwin C, Becker T, Gudnason V, Cruchaga C, Craig D, Amin N, Berr C, Lopez OL, De Jager PL, Deramecourt V, Johnston JA, Evans D, Lovestone S, Letenneur L, Moron FJ, Rubinsztein DC, Eiriksdottir G, Sleegers K, Goate AM, Fievet N, Huentelman MJ, Gill M, Brown K, Kamboh MI, Keller L, Barberger-Gateau P, McGuinness B, Larson EB, Green R, Myers AJ, Dufouil C, Todd S, Wallon D, Love S, Rogaeva E, Gallacher J, St George-Hyslop P, Clarimon J, Lleo A, Bayer A, Tsuang DW, Yu L, Tsolaki M, Bossu P, Spalletta G, Proitsi P, Collinge J, Sorbi S, Sanchez-Garcia F, Fox NC, Hardy J, Naranjo MC, Bosco P, Clarke R, Brayne C, Galimberti D, Mancuso M, Matthews F, Moebus S, Mecocci P, Del Zompo M, Maier W, Hampel H, Pilotto A, Bullido M, Panza F, Caffarra P, Nacmias B, Gilbert JR, Mayhaus M, Lannfelt L, Hakonarson H, Pichler S, Carrasquillo MM, Ingelsson M, Beekly D, Alvarez V, Zou F, Valladares O, Younkin SG, Coto E, Hamilton-Nelson KL, Gu W, Razquin C, Pastor P, Mateo I, Owen MJ, Faber KM, Jonsson PV, Combarros O, O'Donovan MC, Cantwell LB, Soininen H, Blacker D, Mead S, Mosley TH, Jr, Bennett DA, Harris TB, Fratiglioni L, Holmes C, de Bruijn RF, Passmore P, Montine TJ, Bettens K, Rotter JI, Brice A, Morgan K, Foroud TM, Kukull WA, Hannequin D, Powell JF, Nalls MA, Ritchie K, Lunetta KL, Kauwe JS, Boerwinkle E, Riemenschneider M, Boada M, Hiltunen M, Martin ER, Schmidt R, Rujescu D, Wang LS, Dartigues JF, Mayeux R, Tzourio C, Hofman A, Nothen MM, Graff C, Psaty BM, Jones L, Haines JL, Holmans PA, Lathrop M, Pericak-Vance MA, Launer LJ, Farrer LA, van Duijn CM, Van Broeckhoven C, Moskvina V, Seshadri S, Williams J, Schellenberg GD, Amouyel P. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet. 2013.

[72] Lancet. 1998. 351: 1840-1843.

[73] Lathia JD. Alzheimer's Disease: Molecular Mechanisms. American Journal of Neurochemistry. 2008; 107(6): 1471-1481.

[74] Lee G, Cowan N, Kirschner M. The primary structure and heterogeneity of tau protein from mouse brain. Science. 1988; 239: 285– 288.

[75] Leslie C, Eliezer M. Molecular mechanisms of neurodegeneration in Alzheimer's disease. 2010.

[76] Lovestone S, Davis DR, Webster MT. Lithium reduces tau phosphorylation: effects in living cells and in neurons at therapeutic concentrations. Biol Psychiatry. 1999; 45: 995–1003.

[77] Lue L. Alzheimer's Disease Molecular Mechanisms. The American Journal of Pathology. 1999; 155(3): 853-662.

[78] Marlatt MW, Bauer J, Aronica E, Elise S, Haastert V, Jeroen J, Hoozemans M, Joels M, Paul JL. Proliferation in the Alzheimer Hippocampus Is due to Microglia, Not Astroglia, and Occurs at Sites of Amyloid Deposition. 2014.

[79] Maphis NM, Jiang S, Binder J, Wright C, Gopalan B, Lamb BT, Bhaskar K. Whole Genome Expression Analysis in a Mouse Model of Tauopathy Identifies MECP2 AS A Possible Regulator of Tau Pathology. Front. Mol. Neurosci. 17 March 2017.

[80] Masahiro K, Midori K. Link between Aluminum and the Pathogenesis of AD: The Integration of Aluminum and the Amyloid Cascade Hypothesis. Intl. Journal of AD. 8 march 2011.

[81] Matus A. Microtubule-associated proteins: their potential role in determining neuronal morphology. Annu Rev Neurosci. 1988; 11: 29–44.

[82] Maurer K, Volk S, Gerbaldo H. Auguste D and Alzheimer's disease. The Lancet. 1997; 349: 1546-1549.

[83] Maynard CJ. Journal Of Biological Chemistry. 2002; 277(47): 44670-44676.

[84] Medeiros R, Prediger RD, Passos GF, Pandolfo P, Duarte FS, Franco JL, Dafre AL, Di Giunta G, Figueiredo CP, Takahashi RN. Connecting TNF-alpha signaling pathways to iNOS expression in a mouse model of Alzheimer's disease: relevance for the behavioral and synaptic deficits induced by amyloid beta protein. J Neurosci. 2007; 27: 5394-5404.

[85] Meyer-Luehmann M, Spires-Jones TL, Prada C, Garcia-Alloza M, de Calignon A, Rozkalne A, Koenigsknecht-Talboo J, Holtzman DM, Bacskai BJ, Hyman BT. Rapid appearance and local toxicity of amyloid-beta plaques in a mouse model of Alzheimer's disease. Nature. 2008; 451: 720-724.

[86] Michael WM, JB, Eleonora A, Elise S. VH, Jeroen JMH, Marian J, Paul JL. Proliferation in the Alzheimer Hippocampus Is due to Microglia, Not Astroglia, and Occurs at Sites of Amyloid Deposition. Neural Plast. 2014; 693851.

[87] Möller HJ, Graeber MB. The case described by Alois Alzheimer in 1911. Eur Arch Psychiatry Clin Neurosci. 1989; 248: 111-122.

[88] Moss ML, Bomar M, Liu Q, Sage H, Dempsey P, Lenhart PM, Gil - lispie PA, Stoeck A, Wildeboer D, Bartsch JW, Palmisano R, Zhou P. The ADAM10 prodomain is a specific inhibitor of ADAM10 proteolytic activity and inhibits cellular shedding events. J Biol Chem. 2007; 282: 35712-35721.

[89] Nakagawa T. Nature. 2000; 403: 98-103.

[90] Nakata-Kudo Y, Mizuno T, Yamada K, Shiga K, Yoshikawa K, Mori S, Nishimura T, Nakajima K, Nakagawa M. Microbleeds in Alzheimer disease are more related to cerebral amyloid angiopathy than cerebrovascular disease. Dement Geriatr Cogn Disord. 2006; 22: 8-14.

[91] Nature Medicine. (1997). Alzheimer's disease Molecular Mechanisms. 1997; 3(9): 1016-1020.

[92] Nelson TJ. Journal Of Biological Chemistry. 2005; 280(8): 7377-7387.

[93] Neurobiology Of Aging. 2003; 24: 589-596.

[94] Neuroepidemiology. 1992; 13: 131-144.

[95] Oddo S. Proceedings Of The National Academy Of Sciences (USA). 2005; 102(8): 3046-3051.

[96] Ohsawa I, Takamura C, Morimoto T, Ishiguro M, Kohsaka S. Aminoterminal region of secreted form of amyloid precursor protein stimulates proliferation of neural stem cells. Eur J Neurosci. 1999; 11: 1907-1913.

[97] Opazo C. Journal Of Biological Chemistry. 2002; 277(43): 20302-40308.

[98] Palop JJ, Chin J, Roberson ED, Wang J, Thwin MT, Bien-Ly N, Yoo J, Ho KO, Yu GQ, Kreitzer A. Aberrant excitatory neuronal activity and compensatory remodeling of inhibitory hippocampal circuits in mouse models of Alzheimer's disease. Neuron. 2007; 55: 697-711.

[99] Panza F, Lozupone M, Logroscino G, Imbimbo BP. A critical appraisal of amyloid-β-targeting therapies for Alzheimer disease. Nat Rev Neurol. 2019; 15: 73–88.

[100] Pastor P, Ezquerra M, Tolosa E, Munoz E, Marti MJ, Valldeoriola F, Molinuevo JL, Calopa M, Oliva R. Further extension of the H1 haplotype associated with progressive supranuclear palsy. Mov Disord. 2002; 17: 550–556.

[101] Pederson WA, Chan SC, Mark P. A Mechanism for the Neuroprotective Effects of Apolipoprotein E. journal of Neurochemistry. 2002; 74(4).

[102] Pluta R, Ułamek M, Jabłoński M. Consideration of the ischaemic basis and treatment of Alzheimer's disease. Folia Neuropathol. 2010; 48: 11-26.

[103] Pluta R, Jabłoński M, Czuczwar SJ. Postischemic dementia with Alzheimer phenotype: selectively vulnerable versus resistant areas of the brain and neurodegeneration versus β-amyloid peptide. Folia Neuropathol. 2012; 50: 101-109.

[104] Podtelezhnikov AA, Tanis KQ, Nebozhyn M, Ray WJ, Stone DJ.. Molecular Insights into the Pathogenesis of Alzheimer's Disease and Its Relationship to Normal Aging. PLoS ONE. 2011; 6(12): e29610.

[105] Povova J, Ambroz P, Bar M, Pavukova V, Sery O, Tomaskova H, Janout V. Epidemiological of and risk factors for Alzheimer's disease: A review. Biomed Pap Med Fac Univ Palacky Olomouc Czech Republic. 2012; 156: 108-114.

[106] Reiman EM. Proceedings of the National Academy of Sciences (USA). 2001; 98(6): 3334-3339.

[107] Rissman RA. The Journal Of Clinical Investigation. 2003; 114(1): 121-130.

[108] Rutten BPF, Steinbusch HWM. Current Concepts in Alzheimer's Disease: Molecules, Models and Translational Perspectives. 2013.

[109] Sadot E, Gurwitz D, Barg J, Behar L, Ginzburg I, Fisher A. Activation of m(1) muscarinic acetylcholine receptor regulates tau phosphorylation in transfected PC12 cells. J Neurochem. 1996; 66: 877–880.

[110] Sadot E, Heicklenklein A, Barg J, Lazarovici P, Ginzburg I. Identification of a tau promoter region mediating tissue-specific regulated expression in PC12 cells. J Mol Biol. 1996; 256: 805–812.

[111] Salomon AR, Marcinowski KJ, Friedland RP. Nicotine inhibits amyloid formation by the beta-peptide. Biochemistry. 1996; 35:13568-78.

[112] Schmitt FA, Davis DG, Wekstein DR, Smith CD, Ashford JW. ''Preclinical'' AD revisited: neuropathology of cognitively normal older adults. Neurology. 2000; 55: 370–376.

[113] Schmidt AM. Circulation Research. 1999; 84(5): 489-497.

[114] Selkoe DJ. Normal and abnormal biology of the beta-amyloid precursor protein. Annu Rev Neurosci. 1994; 17: 489-517.

[115] Sery O, Povova J, Misek I, Pesak L, Janout V. Molecular Mechanisms of Neuropathological Changes in Alzheimer's Disease: A Review. Folia Neuropathol. 2013; 51(1):1-9.

[116] Sibelerud R, Mutter J, Moore E, Naumann J, Walach H. A Hypothesis and Evidence that Mercury May be an Etiological Factor in Alzheimer's Disease. Int. J Environ Res Public Health. 2019 Dec; 16(24): 5152. 2019 Dec 17. doi: 10.3390/ijerph16245152. PMC 6950077

[117] Simons M. Proceedings of the National Academy of Sciences (USA). 1998; 94(11): 6460-6464.

[118] Simon ML, Eugene H, Sam G, Ralph NM. Expanding the association between the APOE gene and the risk of Alzheimer's disease: possible roles for APOE promoter polymorphisms and alterations in APOE transcription. Journal of Neurochemistry. 2003; 84(6): 1215–1236.

[119] Simard AR, Soulet D, Gowing G, Julien JP, Rivest S. Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer's disease. Neuron. 2006, 49: 489-502.

[120] Spasic D, Raemaekers T, Dillen K, Declerck I, Baert V, Serneels L, Fullekrug J, Annaert W. Rer1p competes with APH-1 for binding to nicastrin and regulates gamma-secretase complex assembly in the early secretory pathway. J Cell Biol. 2007; 176: 629-640.

[121] Stockley JH, O'Neill C. Understanding BACE1: essential protease for amyloid-beta production in Alzheimer's disease. Cell Mol Life Sci. 2008; 65: 3265-3289.

[122] Stone DJ, Molony C, Suver C, Schadt EE, Potter WZ. ApoE genotyping as a progression-rate biomarker in phase II disease-modification trials for Alzheimer's disease. Pharmacogenomics J. 2010; 10: 161–164.

[123] Suzhen D, Yale D, Yinghe H, Zheng Z. Advances in the pathogenesis of Alzheimer's disease: a re-evaluation of amyloid cascade hypothesis. Translational Neurodegeneration 2012; 1: 18.

[124] Thakur AK, Kamboj P, Goswami K. Pathophysiology and management of alzheimer's disease: an overview. J Anal Pharm Res. 2018; 9(2): 226?235.

[125] Tian Y, Crump CJ, Li YM. Dual role of alpha-secretase cleavage in the regulation of gamma-secretase activity for amyloid production. J Biol Chem. 2010, 285: 32549-32556.

[126] Vassar R, Bennett BD, Babu-Khan S, Kahn S, Mendiaz EA, Denis P, Teplow DB, Ross S, Amarante P, Loeloff R, Luo Y, Fisher S, Fuller J, Edenson S, Lile J, Jarosinski MA, Biere AL, Curran E, Burgess T, Louis JC, Collins F, Treanor J, Rogers G, Citron M. Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. Science 1999; 286: 735-741.

[127] Waring SC, Rosenberg RN. Genome-wide association studies in Alzheimer disease. Arch Neurol. 2008; 65: 329–334.

[128] Wolfe MS. Tau mutations in neurodegenerative diseases. J Biol Chem. 2009; 284: 6021–6025.

[129] Wolozin B. Proceedings of the National Academy of Sciences (USA). 2001; 98 (10): 5371-5373.

[130] Xiaoning Bi. Alzheimer's disease: Update on Basic Mechanisms. J Am Osteopathic Assoss. 2010; 110 (9 Suppl 8) S3-S9.

[131] Yamamoto A. Journal Of Neurochemistry. 2002; 82(5): 1137-1147.

[132] Yan R, Bienkowski MJ, Shuck ME, Miao H, Tory MC, Pauley AM, Brashier JR, Stratman NC, Mathews WR, Buhl AE, Carter DB, Tomasselli AG, Parodi LA, Heinrikson RL, Gurney ME. Membrane-anchor - ed aspartyl protease with Alzheimer's disease beta-secretase activity. Nature 1999; 402: 533-537.

[133] Yang Y. The Journal Of Neuroscience. 2003; 23(7): 2557-2563.

[134] Yoshida H, Goedert M. Molecular cloning and functional characterization of chicken brain tau: isoforms with up to five tandem repeats. Biochemistry. 2002; 41: 15203–15211.

[135] Zhao G, Cui MZ, Mao G, Dong Y, Tan J, Sun L, Xu X. gamma-Cleavage is dependent on zeta-cleavage during the proteolytic processing of amyloid precursor protein within its transmembrane domain. J Biol Chem. 2005; 280: 37689-37697.

[136] Zhou Z, Liang Y, Zhang X, Xu J, Lin J, Zhang R, Kang K, Liu C, Zhao C, Zhao M. Low-Density Lipoprotein Cholesterol and Alzheimer's Disease: A Systematic Review and Meta-Analysis. Forn. Aging Neurosci. 30 January 2020.