Alzheimer's Disease and the Amyloid Cascade

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ABSTRACT

Alzheimer's disease is neurodegenerative and may have a sporadic characteristic, often associated with failures in proteostasis, related to the individual's aging processes. It can also present a hereditary contribution, especially in cases where it appears early in patients. The amyloid cascade, which is mainly responsible for the development of the pathology, involves events of fragmentation of the amyloid precursor protein (APP) by peptidases known as beta and gamma secretases, generating an increased amount of a poorly soluble protein fragment, which is deposited in the interneuronal space, forming amyloid plaques. Physiological changes lead to structural changes in tau protein, a component of neuronal microtubules, which when hyperphosphorylated by cell kinases, aggregate to form neurofibrillary tangles. The progression of these protein deposits induces synaptic and neuronal loss, by activating glial cells that release pro-inflammatory cytokines, generating atrophy mainly in the hippocampus and cerebral cortex. The main treatments available so far to control Alzheimer's disease are not very encouraging, since they do not act effectively on amyloidosis. More recent studies involve the production of monoclonal antibodies capable of interacting with protein fragments, breaking down these senile plaques. While they represent a significant advancement, it is important to consider the risks and potential side effects of these medications.

Keywords: Amyloidosis, Aβ42, Thauopathy, Neurodegeneration.

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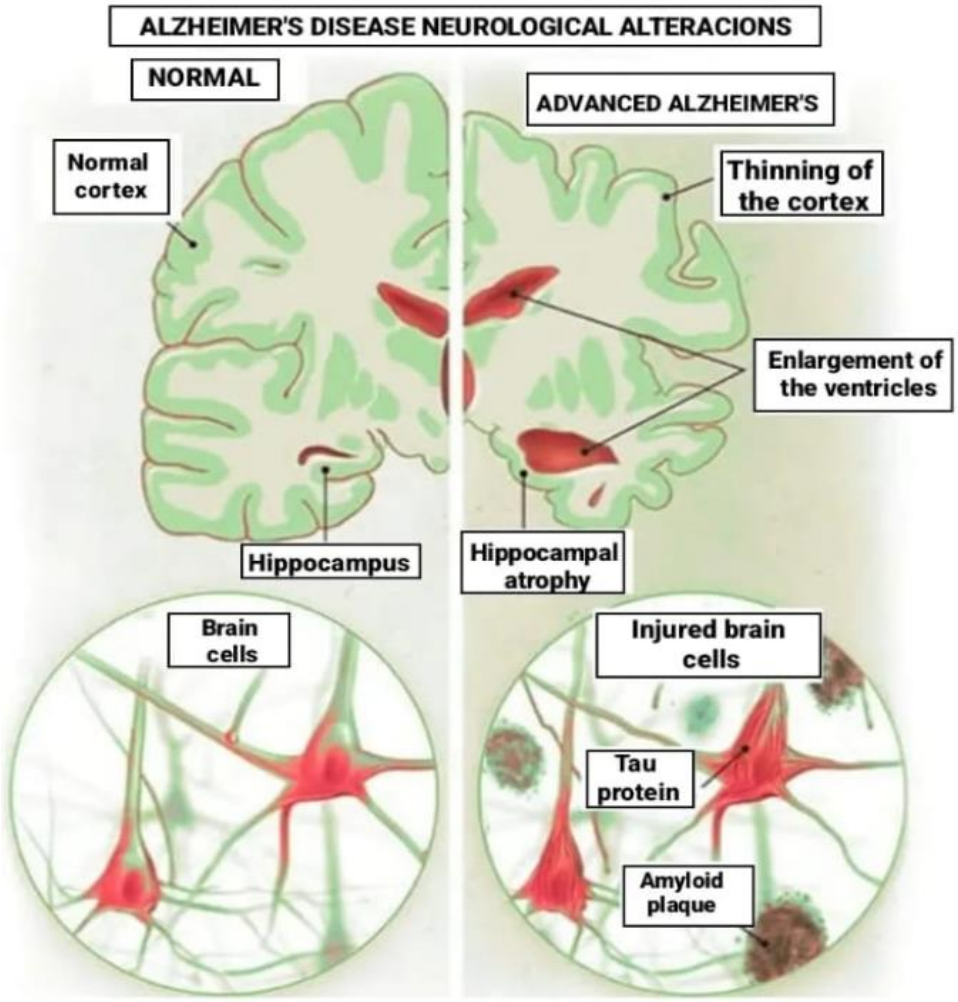
INTRODUCTION

Alzheimer's disease (AD) was identified by psychiatrist Alois Alzheimer in 1906, when describing a form of dementia in a 51-year-old patient who manifested language and memory difficulties with continuous worsening, dying a few years after the onset of symptoms. At necropsy, accumulations of amyloid plaques in the extracellular space and neurofilamentary lesions within neurons throughout the cerebral cortex were observed, distinctive features of Alzheimer's disease, which later received its name due to the suggestion of a German professor of psychiatry named Emil Kraepelin (Souza *et al*., 2021). The disorder is a brain condition that gradually deteriorates memory and reasoning abilities and, over time, compromises the ability to perform the most basic tasks (Alzheimer's and Related Dementias Education And Referral Center, 2021).

It is pathologically characterized by the presence of fibrillary β-amyloid peptide (Aβ) in extracellular senile plaques and tau protein filaments in intracellular neurofibrillary clusters (Rahman; Lendel, 2021) is described as the fifth leading cause of death in the world, affecting approximately 45 million people (Ma; Hong; Yang, 2022).

The leading theory postulates that the degenerative process in AD is triggered by the overproduction and/or reduction of the clearing and subsequent accumulation of β-amyloid peptide (Aβ) in the affected brain tissues, as well as tau protein neurofibrillary tangles (NFEs); accompanied by homeostatic disturbances that result in the disruption of the neuronal cytoskeleton. Amyloid precursor protein (APP) is usually fragmented by the enzyme α-secretase (ADAM-10) to produce soluble peptides (APPs); in AD, alternative and sequential fragmentation occurs by secretases β (BACE-1) and γ, generating insoluble Aβ peptides that aggregate and are deposited in the extracellular space, initiating a sequence of pathological events that lead to the formation of senile or neuritic plaques (NPs) and neuronal death. On the other hand, ENFs are intracellular accumulations composed of hyperphosphorylated tau protein. Typically, *tau protein* maintains the integrity of intraneuronal microtubules, a function that is lost with the process of hyperphosphorylation (Roda *et al*., 2022).

Figure 1: The figure shows the changes that occur in AD. In the upper part of the figure, atrophy in the cortical and hippocampal regions is evidenced, and the growth of the ventricles is also observed. In the lower part of the figure, changes in the extracellular spaces can be seen, with the appearance of amyloid plaques from the deposits of Aβ fragments and the formation of neurofibrils by aggregates of *intraneuronal* tau protein.



Histopathologically, AD is characterized by massive synaptic loss and neuronal death observed in brain regions responsible for cognitive functions, including the cerebral cortex, hippocampus, entorhinal cortex, and ventral striatum. In addition, the brain parenchyma of AD patients has amyloidal fibrillar deposits located in the walls of blood vessels, associated with a variety of different types of senile plaques, accumulation of abnormal tau protein filaments and consequent formation of neurofibrillary tangles-NFT (Figure 1), neuronal and synaptic loss, glial activation, and inflammation (Sereniki, Vital, 2008).

The factors most associated with increased risk for AD are advanced age, female gender, and APOE4 genotype. Other factors that may be involved include family history, depression, low educational attainment, trisomy 21, smoking, diabetes, hypertension, and fatty diet (Caixeta, 2012).

The clinical manifestations of AD can be divided into 4 forms, according to the intensity of manifestation of symptoms (Brazil, 2024):

- Initial: changes in memory, personality, and visual and spatial skills;

- Moderate: difficulty in speaking and performing simple tasks and coordinating movements, as well as agitation and insomnia;
- Severe: resistance to performing daily tasks, urinary and fecal incontinence, difficulty in feeding, and progressive motor impairment;
- Terminal: bed restriction, mutism, pain when swallowing, and intercurrent infections.

The diagnosis of the disease involves the performance of: detailed anamnesis, with evaluation of symptoms, medical and family history; physical and neurological examination with the inclusion of cognitive and functional function tests; complementary exams such as Magnetic Resonance Imaging to evaluate brain atrophy and rule out other forms of dementia; in addition to analyses according to the criteria of the NIA-AA (National Institute on Aging and Alzheimer's Association) and the use of cerebrospinal fluid biomarkers. However, it is important to remember that the definitive diagnosis is the anatomopathological study, not performed *in vivo* (Schilling *et al.*, 2022*).*

Treatment involves pharmacological and non-pharmacological measures (cognitive stimulation, physical activity and emotional support), which aim to control symptoms and delay their progression, with no curative treatment for the disease. The drug classes used are anticholinesterases, glutamate NMDA receptor antagonists, antidepressants (SSRIs) and antipsychotics (preferably atypical) (Greenberg *et al.* 2014).

AMILOIDOSES

Amyloidosis consists of a type of heterogeneous alteration in the three-dimensional structure of proteins, exposing nonpolar amino acids to the external environment and favoring their aggregation, forming insoluble deposits of proteins, both in the intracellular and extracellular environment (Covizzi *et al.*, 2023). Neurodegenerative diseases are characterized by the gradual loss of neurons with cognitive impairment or mobility. The common pathology of these diseases is associated with the abnormal accumulation of misfolded proteins. In neurodegenerative diseases such as Huntington's, Alzheimer's, and Parkinson's, a failure in the protective process of autophagy and proteostasis is observed in maintaining cellular health and preventing the accumulation of these proteins (Panwar *et al.,* 2024).

AD is a progressive and irreversible neurodegenerative disorder, leading to the progressive loss of cognitive functions. Among the main protagonists of this disease are beta-amyloid peptides (Aβ) and *tau* proteins, which play distinct but crucial roles in the development of the disease (Cozachenco *et al.,* 2023). Although the main cause of AD is not yet fully understood, two factors are so far referred to as the crucial players in the disease: amyloid beta plaques and tau tangles. The journey begins with the amyloid precursor protein (APP), present in the cell membrane of healthy neurons. In an ideal physiological scenario, APP is cleaved by the enzymes alpha and gamma-

secretase, releasing soluble fragments that are broken down or recycled by tissues. However, a crucial deviation happens when beta-secretase binds with gamma-secretase, this pathological digestion reaction results in the production of an insoluble peptide called beta-amyloid Aβ (Dawkins, Small, 2014).

Aβ peptides clump together and form beta-amyloid plaques (ABP), which trigger a series of events that are harmful to cells:

- Disruption of Neuronal Signaling: ABPs position themselves between neurons, blocking interneuronal communication, affecting functions such as memory and learning (Hampel *et al.,* 2021).
- Neurotoxic Inflammation: ABPs activate an immune response that leads to neuroinflammation, damaging nearby neurons and exacerbating neurodegeneration (Kempuraj *et al.,* 2017).
- Cerebral Angiopathy: ABPs deposit in blood vessels, causing stiffness and ruptures, impairing cerebral blood flow, and contributing to cognitive dysfunction (Ventura-Antunes *et al.,* 2024).

While ABPs wreak havoc on the outside of cells, inside them, another drama unfolds. Tau proteins, responsible for the structure of microtubules, undergo an abnormal phosphorylation process. This pathological change leads to the formation of neurofibrillary tangles, which:

- Weaken Microtubules: The loss of structural function of microtubules impairs the transport of materials within the cell, affecting its ability to function and contributing to neurodegeneration.
- Induction of Cell Death: Microtubule dysfunction can lead to apoptosis, the programmed death of cells, exacerbating neuronal loss and cognitive decline.

Thus, the relationship between Aβ and *tau* is complex and interdependent. ABPs can trigger abnormal tau phosphorylation, while neurofibrillary tangles can increase Aβ production. This synergistic interaction creates a vicious cycle that accelerates the neurodegeneration and cognitive decline characteristic of AD (Ashrafian *et al.*; 2021).

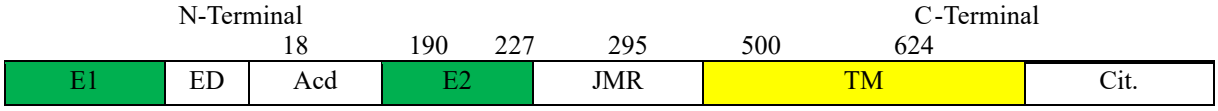
PEPTÍDEO AMILOIDE AB

Amyloid Precursor Protein (APP) belongs to a family of correlated proteins, which includes the Amyloid Precursor Protein-Like Proteins (APLP1 and APLP2) in mammals, and the Amyloid Precursor Protein-Like Protein (APPL) in Drosophila. All these proteins are classified as single-pass transmembranes, presenting extensive extracellular domains. In addition, all of them undergo processing in a manner analogous to APP. It is noted that only APP originates an amyloidogenic fragment, attributable to sequence divergence at the internal site of Aβ (O'brien, Wong, 2011).

Alternative splicing of the APP transcript results in eight isoforms, of which three are the most prevalent: the 695-amino acid form (represented in figure 2), predominantly expressed in the central nervous system, and the 751- and 770-amino acid forms, whose expression is more ubiquitous (Delport, Hever, 2022, O'brien, Wong, 2011). The specific functions of the APP are not yet fully understood. The N-terminal region of the APP begins with the 18th amino acid, since the previous 17 amino acids make up a signal peptide that is removed from the final structure, Among the various domains found in the APP, two heparin-binding regions (E1 and E2), a copper-binding domain (CuBD) in E2, an acidic amino acid region (AcD), the beta-amyloid region that surrounds the JMR (junction) and TM (transmembrane) domains and an intracellular C-terminal domain (Dawkins, Small, 2014, Savonenko *et al.,* 2023).

Map with the domains of Amyloid Precursor Protein (APP)

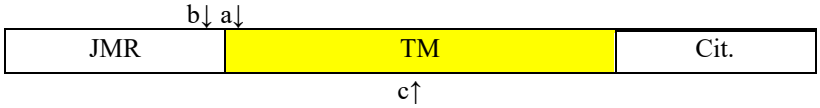
Figure 2: The figure shows the structural domains of the Amyloid Precursor Protein (695 amino acid APP - aa). The upper numbers indicate the amino acids of the sequence, starting from the N-terminus (already removed the signal peptide). At the bottom we observe the different constituent domains of this APP, where E1 (aa. 18-190) and E2 (aa. 295-500), known as folded domains. Between the two domains, we find the ED region (aa. 191-227), called the extension domain, and the acid domain (AcD), characterized by its great flexibility, also observed in the region close to the membrane (JMR). The TM domain is the region of the protein that is associated with the plasma membrane and the Cit domain refers to the cytosolic sequence of the protein.



Sequential cleavage of PPA occurs through two distinct pathways. In one pathway, the APP protein family features extensive biologically active N-terminal ectodomains, as well as a shorter C-terminus that harbors a crucial Tyrosine-Glutamic Acid-Asparagine-Proline-Threonine-Tyrosine (YENPTY) protein classification domain, to which the X11 and Fe65 adaptor proteins bind. The Aβ peptide originates in the ectodomain and extends to the transmembrane region. Following this logic, non-amyloid processing of APP is carried out, which involves α-secretase followed by γ-secretase. In addition, there is amyloid processing of APP, through the action of secretase β followed by the action of γ-secretase (Figure 3). Both processes result in the generation of soluble ectodomains (sAPPα and sAPPβ) and identical intracellular C-terminal fragments (AICD) (Dawkins, Small, 2014, O'brien, Wong, 2011).

Map with the cleavage regions for secretases generating amyloid and non-amyloid peptides.

Figure 3: The figure shows the cleavages made by the secreted enzymes (α, β and γ), generating the non-amyloid peptides, cleaved by α and γ secretases, and amyloid, cleaved by β and γ secretases.



Aβ, with a molecular weight of 4 kDa, originates from amyloid precursor protein (APP), a precursor molecule of greater extent commonly synthesized by brain neurons, vascular cells, blood cells (including platelets) and, to a lesser extent, astrocytes. Aβ is generated by means of two successive proteolytic cleavages of APP, performed by β-secretase (also known as APP-β-1 cleavage enzyme or BACE1) in the ectodomain, forming an intermediate product, which will then be cleaved by γ-secretase in intramembranous sites, generating the peptides Aβ40 (non-toxic) and Aβ42 (toxic) (Sehar *et al.*, 2022, Blennow *et al*., 2006).

A AND B-SECRETASE: STRUCTURE, SUBSTRATES, REGULATION

The enzymes BACE1 and BACE2, encoded by genes on chromosomes 11 and 21, respectively, are transmembrane aspartic proteases directly involved in the cleavage of APP. BACE1 preferentially cleaves APP at the +11 to +1 Aβ sites in APP, being essential for Aβ generation. Significantly, the Swedish mutation of APP (APPswe) is cleaved perhaps 100 times more efficiently at the +1 site than wild APP. Thus, this mutation significantly increases cleavage by BACE1 and is responsible for the elevation of Aβ species in the presence of this mutation. BACE1 expression is increased in certain regions of the brain in some cases of sporadic AD. Therefore, BACE1 is the major neuronal β-secretase and is responsible for pro-amyloid cleavages. BACE2 mRNA, present in several systemic organs, is very low in neural tissues, except for scattered nuclei in the hypothalamus and brainstem. BACE2 activity appears to be virtually undetectable in brain regions involved in AD and is responsible for generating anti-amyloid cleavages at the +19/+20 Aβ positions. Thus, BACE2, an anti-amyloid enzyme, acts as α-secretase, which cleaves between Aβ peptide residues 16 and 17 (Savonenko *et al*., 2023).

Γ-SECRETASE: STRUCTURE, SUBSTRATES, REGULATION

γ-secretase is a complex of membrane proteins that contains four essential subunits: presenilin (PS), nicastrine (Nct), anterior pharynx-defective 1 (Aph1), and presenilin enhancer 2 (Pen2), which catalyzes proteolysis within the transmembrane domain of the substrates. While the catalytic site of the enzyme resides in the PS subunit, sequential assembly of all four essential subunits is required for an active γ-secretase complex (Mattson, 2003). More than 90 substrates have been identified as processed by γ-secretase. Among these substrates, PPA has aroused particular interest due to its relevance in AD and other human disorders. To generate Aβ peptides, APP is

initially cleaved by β-secretase in the extracellular space, producing a 99-residue C-terminal fragment (APP-C99), which is subsequently cleaved by γ-secretase generating an intracellular domain (AICD) and Aβ48 or Aβ49 peptides, subsequently reduced every three or four residues in a helix unwinding model of successive substrate cleavage by γ-secretase (Zhang *et al*., 2023). Thus, the cleavages of Aβ48 produce Aβ45, Aβ42, and Aβ38, while the cleavages of Aβ49 result in the sequential generation of Aβ46, Aβ43, and Aβ40. Among these cleavage products, Aβ42 and Aβ43 are particularly prone to aggregation and the formation of amyloid plaques (Pajak *et al.,* 2016). The amyloid cascade hypothesis has been the guiding mechanism for academic and pharmaceutical research for the past 30 years. Based on this hypothesis, the development of γ-secretase inhibitors and, more recently, α-secretase modulators, is considered an attractive therapeutic opportunity for AD (Savoneko *et al*., 2023).

Although a significant part of Aβ is released into the extracellular medium after proteolytic processing of mature APP in the plasma membrane, it can be taken up again by cells. There is evidence that Aβ can also be generated through proteolysis of APP from intracellular membranes such as the endoplasmic reticulum (ER) or the trans-Golgi network. As a result, although it is still conjecture, it is possible that Aβ may escape the secretory pathway, ending up in the cytosol (Ring et al., 2022).

In addition, intracellular Aβ has been identified in several regions of the cytoplasm, including endosomes, multivesicular bodies, lysosomes, mitochondria, endoplasmic reticulum, Golgi, and cytosol, where it interferes with the functions of several organelles. Intracellular Aβ42 oligomers, detectable in brain homogenates of patients with Alzheimer's disease, usually range from dimeric to dodecamers, and may represent the major neurotoxic forms of Aβ peptides. It is noteworthy that neurotoxicity induced by intracellular Aβ42 is associated with mitochondrial dysfunction and increased production of reactive oxygen species (Ring *et al*., 2022).

INTERLACED NEUROFIBRILS OF *TAU PROTEIN*

The *tau* protein is from the class of microtubule-associated proteins (MAP), whose main function is to stabilize them by aggregating tubulin, is found in axons (in healthy cells) or distributed in the cell body and dendrites (in cases of taupatia) and is associated with the development of dementia (Wegmann *et al*., 2021). In the human brain, tau protein is soluble and can be present in 6 isoforms, and the expression of these is regulated during development. In addition, it promotes interaction between actin, neurofilaments, and cytoplasmic organelles, allowing the connectivity of microtubules with cytoskeletal components and mitochondria (Guo *et al.,* 2017).

Microtubules are structures related to the process of cell division, however, when dealing with post-mitotic neurons, microtubules contribute to the maintenance of cytoarchitecture and

intraneural transport that involves the axonal transport of organelles and vesicles, in which neurotransmitters and proteins are displaced to distal synapses. They can be found uniformly in axons by the action of tau protein and, in different ways in dendrites, being stabilized by tubulin. The *tau protein* plays an important role related to tubulin, since when the proteins interact with each other, there is a promotion of greater stability. However, when there is an accumulation of abnormal hyperphosphorylated tau protein due to increased taukinase activity and/or undersensitization of its phosphatases, its tubulin-binding capacity is compromised, destabilizing microtubules in addition to compromising axonal transport and synapse metabolism, causing loss of cell viability, microtubular cytoskeletal collapse, and neuronal death (Wegmann *et al*., 2021, Rawat *et al*., 2022). It is also observed that *the tau protein* is crucial for the stability of neurons, which plays a central role in the pathogenesis of AD when it undergoes pathological changes, such as hyperphosphorylation and aggregation into insoluble structures (Wegmann, 2021).

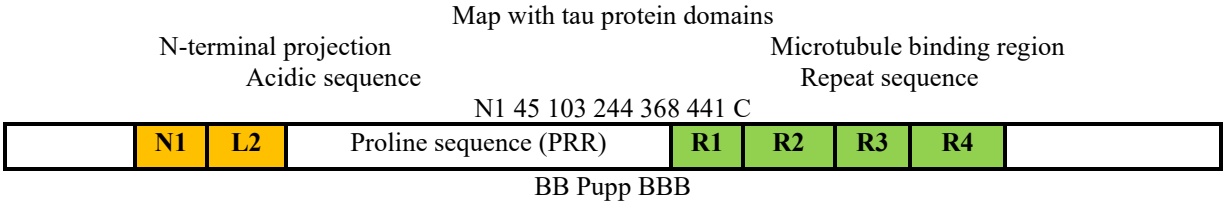
Tau proteins are found predominantly in the axonal part of the neuron and are responsible for the stability and assembly of the microtubule protein. The six different isoforms are produced by alternative splicing of the microtubule-associated tau protein (MAPT) gene, each with its own specific characteristics and functions. The isoforms are differentiated by the presence or absence of three repeat domains (3R or 4R) and by the presence or absence of sequences encoded by exons 2 and 3. The ratio of 3R and 4R isoforms in the normal human brain is 1:1, while in several taupathies, this ratio changes (Roda, *et al*. 2022).

It is also worth mentioning the importance of tau haplotypes and impact on susceptibility to the disease, as the MAPT gene, responsible for encoding the *tau* protein, has two main haplotypes: H1 and H2. The H1 haplotype is associated with several neurodegenerative disorders, while the H2 has a reduced risk for these diseases (Kent *et al.*, 2020).

Each isoform has four parts (Figure 4):

- N-terminal projection domain: Determines the regulation of the distance between microtubules.
- Proline-rich domain (PRR): Aids in cell signaling, interaction with protein kinases, and contains abundant phosphorylation sites.
- MTBR domain: Contains three or four replicates that bind to the RRP.
- C-terminal domain: Involved in the polymerization of microtubules.

Figure 4: Sequence of 441 amino acids corresponding to *tau* protein. The N-terminal projection begins at the first amino acid of the sequence (aa1), and is characterized by finding two repeated sequences of amino acids of acidic character (aa45 - aa103). In the central region there is a domain rich in amino acids proline (PRR) and a little further to the right we find the PPR binding repeats (R1-R4). The C-terminal portion is known as the microtubule-binding region (aa368-441). The phosphorylation points are indicated by the letter P.



In AD, *the tau* protein undergoes pathological changes that make it dysfunctional and contribute to neurodegeneration. The main pathological features of *tau* in AD include:

- Hyperphosphorylation: The abnormal phosphorylation of *tau* at specific sites separates it from the microtubules, destabilizing the neuronal structure.
- Aggregation in Paired Helical Filaments (PHFs) and Neurofibrillary Tangles (NFTs): Hyperphosphorylated tau aggregates into insoluble structures, forming PHFs and NFTs, which accumulate in neurons and compromise their function.
- Altered Protein Degradation: The cell's ability to degrade abnormally phosphorylated and aggregated tau is compromised, leading to the accumulation of these pathological proteins (Saito *et al*., 2021).

Tau protein dysfunction in AD leads to several consequences for neuronal cells, including (Rawat *et al.,* 2022):

- Destabilization of Microtubules: The loss of tau stabilizing function leads to disorganization of the neuronal cytoskeleton, affecting intracellular transport and communication between neurons.
- Mitochondrial Dysfunction: Hyperphosphorylated tau interferes with mitochondrial function by impairing energy production and increasing oxidative stress.
- Synaptic Impairment: Tau dysregulation impairs communication between neurons, leading to the loss of synapses and deterioration of cognitive function.
- Cell Death: Tau dysfunction, in conjunction with other pathogenic factors, leads to progressive neuronal death, characterizing neurodegeneration in AD.

In view of the above, tau protein may be associated with the development of other neurodegenerative diseases (taupathies), in addition to AD, it also participates in alpha-synucleinopathies such as Parkinson's Disease (Oliveira *et al.,* 2024).

INFLAMMATION AND MICROGLIA

Neuroinflammation represents a complex biological process and has been seen as an important factor promoting age-related neurodegenerative diseases, such as AD (Kumar, 2018; Wang, 2020).

It is known that the characteristic neurodegenerative condition in AD is associated with the presence of extracellular β-amyloid protein (Aβ) deposit, forming amyloid or neuritic plaques and intracellular neurofibrillary tangles, responsible for neural deterioration. However, currently, such mechanisms are not sufficiently satisfactory for understanding the pathophysiology of Alzheimer's disease, reinforcing the theories of neural neuroinflammation (Câmara, 2019).

The accumulation of intra- and extracellular proteins ends with activation of the immune response, with direct involvement of the innate response, with the release of pro-inflammatory factors by astrocytes and activation of the complement system by microglia. In this mechanism, Interleukins (IL-1B, IL-6, IL-12) and Tumor Necrosis Factor-alpha (TNF-α) play a special role (Câmara, 2019; Machado, Carvalho, Rocha Sobrinho, 2020).

According to Tuppo and Arias (2005), inflammation in Alzheimer's disease, when it becomes chronic, is characterized by the prolonged activation of defense cells of the central nervous system, specifically microglia, promoting the release of inflammatory substances, such as cytokines and free radicals, which can damage healthy neurons, promoting the progression of the disease. In addition, microglial dysfunction in Alzheimer's disease can lead to an imbalance of the brain environment. Normally, microglia play an important role in removing β-amyloid proteins and maintaining homeostasis.

However, at the same time that chronic inflammation is a consequence of protein accumulation, it can also be seen as a cause, creating a vicious cycle, which explains the progressive pattern of the disease (Sereniki; Vital, 2008).

According to Câmara (2019), there are several causes that microglial activation and chronic inflammatory response can contribute to the progression of Alzheimer's disease. The toxicity of cytokines and free radicals as a consequence of the inflammatory response; The destruction of amyloid-β plaques by microglia can accelerate the uncontrolled inflammatory response, causing further neural damage; the dysfunction of microglia in the removal of β-amyloid plaques leading to excessive accumulation of these proteins in the brain, which can contribute to the formation of neurofibrillary plaques and tangles; the production of additional toxic substances, such as reactive oxygen species (ROS), superoxide radicals (· $O2^-$), hydroxyl (· OH^-), and hydrogen peroxide (H2O2), and nitrogen peroxide (RNS) such as nitric oxide (NO) and peroxynitrite ($ONOO^-$), which can cause oxidative and nitrosative damage and stress to neurons and aggravate the progression of Alzheimer's disease; the influence on synaptic function: Chronic inflammation and activation of

microglia can also negatively affect synaptic function in the brain, which can contribute to the cognitive symptoms of Alzheimer's disease; the production of tumor necrosis factor-alpha (TNF-α), a pro-inflammatory cytokine that plays an important role in the inflammatory response and may also contribute to the progression of AD. TNF-α can induce cell death, increase vascular permeability, and promote the production of other inflammatory cytokines; the production of interleukin-1 beta (IL-1β), which plays a key role in regulating the immune and inflammatory response, contributing to neuroinflammation and disease progression.

Finally, Resende and Brand (2022) report that although neuroinflammation can be seen as part of the degenerative process, there is still evidence of a primary genetic factor involved, the *Triggering receptor expressed on myeloid cells 2* (TREM-2) gene, which may be related to microglial activation, a pathology mediated by amyloid protein or TAU protein. This gene produces a protein that regulates the functioning of myeloid cells, stimulating microglial activation, phagocytosis and CNS survival. However, there are variants of the TREM-2 gene region, and R47H is relevant for Alzheimer's Disease. The TREM-2 region is considered to be of paramount importance for the homeostasis of the nervous tissue itself, as it allows microglial cells to be able to control the initial formation and progression of β-amyloid plaques. TREM-2 deficiency also leads to an increase in the deposit of Tau protein and increases the dystrophy of the neurites that are found near the plaques.

GENETICS

Alzheimer's Disease (AD), a neurodegenerative disorder that presents advanced age as the main risk factor, however the genetic influence cannot be ignored. AD can be caused by genetic inheritance or sporadically.

The hereditary pattern accounts for about 5% of Alzheimer's cases, with mutations in specific genes (Table 1) significantly increasing the risk of developing the disease, and this familial form of AD usually presents at younger ages, before age 65. In addition, the sporadic pattern represents about 95%, with no evident family history. This means that the disease develops due to a combination of genetic and environmental factors throughout the individual's life (Fridman *et al*., 2004). Approximately 35 to 60% of patients presenting with early AD have first-degree relatives with dementia, including 10 to 15% from autosomal dominant families with three generations or more (Hoogmartens *et al*., 2021).

The main genes involved in AD are APOE, PSEN1 and PSEN2, and APP (Neuner *et al*., 2020) The APOE gene encodes apolipoprotein E, a protein crucial for lipid transport in the brain. The most common APOE mutation, known as APOE4, is a strong risk factor for AD, especially in the sporadic form. Individuals with two copies of APOE4 have a significantly higher risk of developing

the disease compared to those who have only one or no copies. In addition, the APOE gene has three important alleles, ε2, ε3 and ε4, in which patients with the ε4 allele contain an increased risk of developing AD, and with the e2 allele have a lower risk (Fortea *et al*., 2024).

Table of genes involved with Alzheimer's Disease.

Table 1: The table lists the main genes associated with early AD cases, chromosomal location, inheritance pattern, and the main pathways affected. (Hoogmartens et al., 2021 modified).

Gene	Location	Inheritance	Affected roads
APOE	**19q13.2**	**Modifier**	**Amyloid pathway, immunity, synaptic plasticity, lipid transport, tau pathway , apoptosis, phagocytosis, and autophagy.**
APP	**21q21.3**	**Dominant, de novo recessive/mosaicism**	**Amyloid pathway, BHE integrity, immunity, synaptic plasticity, tau pathway , apoptosis, phagocytosis, and autophagy.**
PSEN1	**14q24.3**	**Dominant, de novo recessive/mosaicism**	**Amyloid pathway, BHE integrity, immunity, synaptic plasticity, apoptosis, phagocytosis, and autophagy.**
PSEN2	**1q31-q42**	**Dominant de novo/mosaicism**	**Via amyloid, immunity, synaptic plasticity, apoptosis, phagocytosis, and autophagy.**
TRAIN2	**6p21.1**	**Dominant**	**Amyloid pathway, immunity, lipid metabolism, synaptic plasticity, apoptosis, phagocytosis, and autophagy.**
ABCA7	**19p13.3**	**Dominant**	**Amyloid pathway, immunity, lipid metabolism, synaptic plasticity, apoptosis, phagocytosis, and autophagy.**

The PSEN1 and PSEN2 genes provide instructions for the production of presenilin proteins, which are essential for the processing of amyloid beta (Aβ) protein. Mutations in these genes can lead to abnormal accumulation of Aβ in the brain, one of the main neuropathological features of AD. The APP gene, on the other hand, encodes the amyloid precursor protein (APP), which is cleaved by presenilins to generate Aβ. Mutations in APP may also increase the risk of AD (Fridman, *et al*. 2004, Valdes *et al.,* 2022).

In addition, there are other genes involved in the development of AD, such as myeloid-expressed screening receptor 2 (TREM2), Serossine Receptor 2 (SORCS2) and the ATP-Binding Cassette Transporter 7 (ABCA7). Mutations in the TREM2 gene may increase the risk of late AD. Mutations in the SORCS2 gene can increase the risk of sporadic AD. In addition, mutations in the

ABCA7 gene can increase the risk of familial AD (Fridman *et al*., 2004). About the main genes associated with AD risk, such as the APP, APOE4 and PSEN1 and PSEN2 genes, in which mutations in the APP gene can lead to the accumulation of amyloid plaques in the brain, one of the main pathological signs of AD. Furthermore, mutations in the PSEN1 and PSEN2 genes can lead to the formation of amyloid plaques and neurofibrillary tangles (Fortea *et al*., 2024). There are other genes that seem to be involved in this pathology. Studies carried out by Bellenquez et al. (2022), totaling 111,326 AD cases against 677,663 controls, showed the probable existence of 75 risk *loci* for AD, where 42 were new.

THERAPY

Despite advances in understanding the pathophysiology of the disease, the therapeutic options currently available are limited to five drugs including tacrine, donepezil, rivastigmine, galantamine, and memantine (Vaz, Silvesre, 2020, Thoe *et al*., 2021). The first four are acetylcholine esterase inhibitors (AchEIs), while the last is an N-methyl-D-aspartate receptor antagonist, exerting the function of relieving the symptoms of the disease, but not incapable of slowing its progression.

Given the need for disease-modifying therapies, immunotherapy emerges as a promising strategy, using the power of the patient's own immune system to fight the pathological proteins that characterize AD. This innovative approach aims to directly attack β-amyloid (Aβ) and *tau* fragments, which accumulate in neurons and contribute to neurodegeneration. This methodology involves designing synthetic peptides or monoclonal antibodies (Leisher *et al*., 2023) to decrease the Aβ load in the brain and slow disease progression.

There are several types of pharmacological therapies that aim to improve the quality of life of the patient affected by AD. Pharmacological treatment aims to stabilize cognitive and behavioral impairment, in addition to modifying other manifestations of the disease, with minimal side effects, but do not result in regression of the signs and symptoms of AD.

Currently, there are many promising studies based on immunotherapy in AD. This promotes an immune response against an autoantigen, with the targets of this therapy being the inhibition of the accumulation of Aβ42 deposition, corresponding to the main peptide found in senile plaques, and also hyperphosphorylated tau, which, in turn, is responsible for forming neurofibrillary tangles inside the nerve cell, being related to the progression of dementia. Inhibiting the accumulation of these proteins can reduce amyloid levels in the brain, as well as remove senile plaques, promoting a significant effect on memory.

B-AMYLOID PEPTIDE VOIDS

The first clinical trial with the AN-1792 vaccine, in which patients received injections of Aβ1-42 peptide, resulted in stimulation of the humoral response, which resulted in a reduction in Aβ and cerebral senile plaques. However, due to negative side effects, such as cases of meningoencephalitis, the study was interrupted (Silva *et al*., 2020, Sousa, 2017).

Although the AN-1792 peptide vaccine failed in clinical trials, it inspired the second generation of Aβ peptide vaccines. In order to establish the decline and prevent the progression of AD, new research with second-generation vaccines has been proposed, aiming to minimize side effects and develop more effective therapies (Alves *et al.* 2023; Parrocha, Nowick, 2023). However, the second-generation vaccines developed have also manifested, in some cases, side effects such as fatigue, nasopharyngitis, myalgias and nausea (Silva Neto, 2014).

CAD-106 (Amilomotide: Novartis Pharmaceuticals) was the only second-generation peptide vaccine that demonstrated greater efficacy in the treatment of AD, with greater tolerance and good immune activation. However, the study was also interrupted by adverse effects in the control group. Several studies, already closed, with different vaccines such as ACI-24 (AC Immune, Roche and Genentech), ABvac40 (Axon Neuroscience SE) and UB-311 (Vaxxinity) have not obtained the desired success in the treatment and progression of AD (Alves *et al.*, 2023; Parrocha, Nowick, 2023).

TAU PEPTIDE VACCINES

In view of the discouraging results of studies with β-amyloid peptide vaccines, new studies have emerged based on Tau peptide vaccines, such as ACI-35 (AC Immune and Janssen) (Asuni *et al.,* 2007), and AADvac1 (Axon Neuroscience) (Parrocha, Nowick, 2023).

ACI-35 resulted in a weak immune response, even with the administration of booster doses. An improved formulation of the vaccine was later developed, ACI-35.030, with a second adjuvant and helper T cell epitopes and demonstrated high titers and specific antibodies to phosphorylated tau and aggregated tau (Parrocha, Nowick, 2023).

AADvac1 (Axon Neuroscience), after phase I clinical trials, promoted an increase in titers against AADvac1 in patients, without signs of brain inflammation. However, these vaccines have not shown improvements in cognitive impairment (Parrocha, Nowick, 2023).

IMUNOTERAPIA B-AMILOIDE

Passive Aβ immunotherapy is based on the use of monoclonal or polyclonal antibodies, with direct intravenous injection, allowing treatment to be interrupted if adverse reactions arise, and to label specific epitopes or pathogenic conformations. Antibody therapy allows for the activation of microglia for antibody facilitation and aggregation inhibition (Spillere, 2015).

According to Alves et al. (2023), the mechanisms of action of antibodies can be:

- Antibodies that recognize the N-terminal epitope in monomers, oligomers and aggregated forms;
- Antibodies that recognize the central epitope of Aβ, only bind to monomers because in oligomers and aggregates the epitope is not "visible";
- Polyclonal antibodies that recognize multiple epitopes in all forms of Aβ (Santos, 2016).

After several studies with mice using antibodies with good performance, several molecules were developed. Among them is Bapineuzumab, the first humanized monoclonal antibody. Although it has bound to plaques and Aβ deposits, it has not proven sufficient efficacy and clinical benefits, as well as adverse reactions (Pereira, 2013).

Other antibodies were developed in an attempt to control the evolution of signs and symptoms, in addition to obtaining cognitive regression in AD. Lilly's Solanezumab (Spillere, 2015), Hoffmann-La Roche's Gantenerumab, is the only human monoclonal antibody that recognizes two Aβ epitopes and binds to fibrillar forms and brain amyloid plaques, inducing phagocytosis by microglia, causing a decrease in Aβ in the brain (Santos, 2016), Genentech's Crenezumab is a humanized monoclonal antibody that has undergone modifications and carries the IgG4 isotype, which gives it low affinity with leukocytes and therefore low possibility of activating the inflammatory immune response, and prevents aggregation and enables the disaggregation of tangles, presenting satisfactory results so far; Gammagard from Baxter International is a polyclonal antibody from healthy donors and has shown decreased serum Aβ levels, however, absence of satisfactory benefits (Sant'ana *et al*., 2018), Aducanumab (BIIB037), demonstrated in clinical trials, a decrease in Aβ plaques in patients with AD onset, while in the placebo group they remained stable. However, there were manifestations of adverse reactions, Octafarma's Octagam uses the same line of research of intravenous immunoglobulins with acceptable safety levels and continuity in studies for better conclusions (Alves, *et al.* 2023). The results of the randomized clinical trial that included 1736 patients with early symptomatic AD and tau amyloid pathology, carried out by Sim (2023) and collaborators, showed that after 76 weeks of treatment with donanemab, clinical progression significantly slowed down.

INIBITORS AND MODULATORS OF SECRET ENZYMES

The amyloid hypothesis is supported by the sequential cleavage of APP by β-secretase and γ-secretase (Hampel, *et al.* 2021). Consequently, the inhibition of these enzymes has been considered an important object of study. γ-secretase is not specific for APP cleavage, acting on other transmembrane proteins, which rules out its use as an appropriate target for treatment. Two secretase

inhibitors are in the study phase. Elenbecestat [E2609] is in phase 2 and Umibecestat [CNP520] is in phase 3, the latter being studied in asymptomatic individuals who have a genetic predisposition due to heterozygosis or homozygosis for APOE4, with elevated amyloid detected by cerebrospinal fluid (Yiannopoulou, 2020). The non-amyloid pathway is promoted by the cleavage of APP by α-secretase and, consequently, its activation is also an important therapeutic target. It is believed that this enzyme is promoted by the phosphatidylinositol 3-kinase (PI3K)/Akt pathway that can be signaled by the GABA receptor. Etazolate [EHT0202] acts as a selective modulator of GABA receptors, however, phase 3 studies have not progressed (Yiannopoulou, 2020).

FINAL CONSIDERATIONS

The growth in life expectancy of the population has favored the prevalence of some neurodegenerative and amyloidogenic dementias such as AD. Different theories to explain this pathology have been raised, such as the cholinergic, amyloidgenic, metallic, and type 3 diabetes hypothesis (De Falco *et al*., 2015). The most studied hypothesis is that of the amyloid cascade, where deficiencies in proteostasis systems involving the processing of the APP protein located in the membrane of neurons would lead to the generation of a fragment of 42 amino acids (Aβ42) that acquires a secondary configuration in β-pleated leaf that ends up forming large protein aggregates. In addition, hyperphosphorylation of the *tau* component of microtubules favors the formation of intracellular interlaced tangles, activating inflammatory processes and production of reactive oxygen and nitrogen species, which culminate in neuronal death and brain atrophy. The initial symptoms involve memory loss and changes in behavior and in the final stages a marked cognitive decline is observed that interferes with most daily activities. Treatment with acetylcholinesterase inhibitors and N-methyl-D-aspartic acid antagonists (memantine) bring relief to symptoms, but do not delay the progress of the disease (Luo, Li, 2022). Treatment by vaccines against the Aβ peptide has not yet demonstrated effective results, however monoclonal antibody therapy seems to have more consistent results. These agents interfere with the progression of pathogenic steps responsible for clinical symptoms, including amyloid plaque deposition and neurofibrillary tangles. Modulating agents of the secretory enzymes that control amyloid and non-amyloid pathways have been studied. Other therapies include neuroprotective agents, anti-inflammatory growth factor promoters, effective metabolic agents, and stem cell utilization (Yiannopoulou, Papageorgiou, 2020).

REFERENCES

1. Alves, D. E., Damião, B., & Simioni, P. U. (2023). Doença de Alzheimer: uma atualização sobre tratamentos e perspectivas. *Cadernos Acadêmicos, 9*(1), 87-100. https://portaldeperiodicos.animaeducacao.com.br/index.php/CA/article/view/18855. Acesso em 18/07/2024.

2. Alzheimer's and Related Dementias Education and Referral Center. (2021). *Alzheimer´s Disease* (NIH Publication No. 21-AG-6423). https://www.nia.nih.gov/health/alzheimers-and-dementia/about-adear-center. Acesso em 26/06/2024.

3. Ashrafian, H., Zadeh, E. H., & Khan, R. H. (2021). Review on Alzheimer's disease: Inhibition of amyloid beta and tau tangle formation. *International Journal of Biological Macromolecules, 167*, 382–394. https://doi.org/10.1016/j.ijbiomac.2020.11.192

4. Asuni, A. A., Boutajangout, A., Quartermain, D., & Sigurdsson, E. M. (2007). Immunotherapy targeting pathological tau conformers in a tangle mouse model reduces brain pathology with associated functional improvements. *Journal of Neuroscience, 27*(34), 9115-9129. https://doi.org/10.1523/JNEUROSCI.2361-07.2007

5. Bellenguez, C., Küçükali, F., Jansen, I. E., et al. (2022). New insights into the genetic etiology of Alzheimer's disease and related dementias. *Nature Genetics, 54*, 412–436. https://doi.org/10.1038/s41588-022-01024-z

6. Blennow, K., de Leon, M. J., & Zetterberg, H. (2006). Alzheimer's disease. *Lancet, 368*(9533), 387-403. https://doi.org/10.1016/S0140-6736(06)69113-7

7. Brasil. (2024). Saúde de A a Z. Alzheimer. https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/a/alzheimer. Acesso em 17/07/2024.

8. Caixeta, L. (2012). *Doenças de Alzheimer*. Porto Alegre: Artmed: Grupo A. E-book.

9. Camara, A. B. (2019). Receptores neurais e a doença de Alzheimer: uma revisão sistemática da literatura sobre as famílias de receptores mais associadas à doença, suas funções e áreas de expressão. *Jornal Brasileiro de Psiquiatria, 68*(3), 161-176. https://www.scielo.br/j/jbpsiq/a/XCn9FKP5q6LPg4NNgW3qsJy/?format=pdf&lang=pt. Acesso em 26/04/2024.

10. Covizzi, I. V. B., Scalon, T., Villas Boas, J. R., Oliveira, I. C., Santos, T. A., Lima, A. R. de A., & Covizzi, U. D. S. (2023). *The incorrect folding of proteins and their involvement with pathological processes*. Seven Editora. https://doi.org/10.56238/innovhealthknow-033

11. Cozachenco, D., Ribeiro, F. C., & Ferreira, S. T. (2023). Defective proteostasis in Alzheimer's disease. *Ageing Research Reviews, 85*, 101862. https://doi.org/10.1016/j.arr2023.101862

12. Dawkins, E., & Small, D. H. (2024). Insights into the physiological function of the β-amyloid precursor protein: Beyond Alzheimer's disease. *Journal of Neurochemistry, 129*, 756-776. https://doi.org/10.1111/jnc.12675

13. De Falco, A., Cukierman, D. S., Hauser-Davis, R. A., & Rey, N. A. (2015). Alzheimer's disease etiological hypotheses and treatment perspectives. *Química Nova*. https://doi.org/10.5935/0100-4042.20150152

14. Delport, A., & Hewer, R. (2022). The amyloid precursor protein: A converging point in Alzheimer's disease. *Molecular Neurobiology, 59*, 4501–4516. https://doi.org/10.1007/s12035-022-02863-x

15. Fortea, J., Pegueroles, J., Alcolea, D., et al. (2024). APOE4 homozygosity represents a distinct genetic form of Alzheimer's disease. *Nature Medicine, 30*, 1284–1291. https://doi.org/10.1038/s41591-024-02931-w

16. Fridman, C., Gregório, S. P., Dias Neto, S. P. E., & Ojopi, E. P. B. (2024). Alterações genéticas na doença de Alzheimer. *Archives of Clinical Psychiatry, 31*(1), 19–25. https://www.scielo.br/j/rpc/a/rPRVRPvHV6d7gJ3z4SNP7YL/. Acesso em 18/07/2024.

17. Greenberg, D. A., Aminoff, M. J., & Simon, R. P. (2014). *Neurologia clínica*. Porto Alegre: Artmed: Grupo A. E-book. ISBN 9788580553550.

18. Guo, T., Noble, W., & Hanger, D. P. (2017). Roles of tau protein in health and disease. *Acta Neuropathologica, 133*(5), 665-704. https://doi.org/10.1007/s00401-017-1707-9

19. Hampel, H., Hardy, J., Blennow, K., et al. (2021). The Amyloid-β pathway in Alzheimer's disease. *Molecular Psychiatry, 26*, 5481–5503. https://doi.org/10.1038/s41380-021-01249-0

20. Hoogmartens, J., Cacace, R., & Van Broeckhoven, C. (2021). Insight into the genetic etiology of Alzheimer's disease: A comprehensive review of the role of rare variants. *Diagnosis, Assessment & Disease Monitoring*, 1-14. https://doi.org/10.1002/dad2.12155

21. Kempuraj, D., Thangavel, R., Selvakumar, G. P., Zaheer, S., Ahmed, M. E., Raikwar, S. P., Zahoor, H., Saeed, D., Natteru, P. A., Iyer, S., & Zaheer, A. (2017). Brain and peripheral atypical inflammatory mediators potentiate neuroinflammation and neurodegeneration. *Frontiers in Cellular Neuroscience, 11*, 1-16. https://doi.org/10.3389/fncel.2017.00216

22. Kent, S. A., Spires-Jones, T. L., & Durrant, C. S. (2020). The physiological roles of tau and Aβ: Implications for Alzheimer's disease pathology and therapeutics. *Acta Neuropathologica, 140*, 417–447. https://doi.org/10.1007/s00401-020-02196-w

23. Kumar, A. (2018). Neuroinflammation and cognition. *Frontiers in Aging Neuroscience, 10*, 413. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6297877/pdf/fnagi-10-00413.pdf

24. Leisher, S., Bohorquez, A., Gay, M., et al. (2023). Amyloid-lowering monoclonal antibodies for the treatment of early Alzheimer's disease. *CNS Drugs, 37*, 671–677. https://doi.org/10.1007/s40263-023-01021-8

25. Luo, J. E., & Li, Y. M. (2022). Turning the tide on Alzheimer's disease: Modulation of γ-secretase. *Cell Bioscience, 12*(2), 2-12. https://doi.org/10.1186/s13578-021-00738-7

26. Ma, C., Hong, F., & Yang, S. (2022). Amyloidosis in Alzheimer's disease: Pathogeny, etiology and related therapeutic directions. *Molecules, 27*, 1210. https://doi.org/10.3390/molecules27041210

27. Machado, A. P. R., Carvalho, I. O., & Rocha Sobrinho, H. M. (2020). Neuroinflamação na doença de Alzheimer. *Revista Brasileira Militar de Ciências, 6*(14), 30-38. https://doi.org/10.36414/rbmc.v6i14.33. https://rbmc.emnuvens.com.br/rbmc/article/view/33

28. Mattson, M. (2003). Ballads of a protein quartet. *Nature, 422*, 385–387. https://doi.org/10.1038/422385a

29. Neuner, S. M., Julia, T. C. W., & Goate, A. M. (2020). Genetic architecture of Alzheimer's disease. *Neurobiology of Disease, 143*, 104976. https://doi.org/10.1016/j.nbd.2020.104976

30. O'Brien, R. J., & Wong, P. C. (2011). Amyloid precursor protein processing and Alzheimer's disease. *Annual Review of Neuroscience, 34*(1), 185–204. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3174086/

31. Oliveira, I. C., Santos, T. A., Covizzi, I. V. B., Scalon, T., Villas Boas, J. R., Andrade, F. E. C., Lima, A. R. de A., Vayego, S. A., & Covizzi, U. D. S. (2024). α-Synuclein aggregates and Parkinson's disease. *Seven Editora*, 703–719. https://doi.org/10.56238/sevened2024.001-055

32. Pajak, B., Kania, E., & Orzechowski, A. (2016). Killing me softly: Connotations to unfolded protein response and oxidative stress in Alzheimer's disease. *Oxidative Medicine and Cellular Longevity*. Hindawi Publishing Corporation, 1-17. https://doi.org/10.1155/2016/1805304

33. Pereira, P. M. C. M. (2013). *Doença de Alzheimer: Perspetivas de tratamento*. (63 f.). Dissertação (Mestrado) - Curso de Ciências Médicas, Universidade da Beira Interior, Covilhã. http://hdl.handle.net/10400.6/1484

34. Parrocha, C. M. T., & Nowick, J. S. (2023). Current peptide vaccine and immunotherapy approaches against Alzheimer's disease. *Peptide Science, 115*(1), e24289. https://doi.org/10.1002/pep2.24289

35. Rahman, M. M., & Lendel, C. (2021). Extracellular protein components of amyloid plaques and their roles in Alzheimer's disease pathology. *Molecular Neurodegeneration, 16*(59). https://doi.org/10.1186/s13024-021-00465-0

36. Rawat, P., Sehar, U., Bisht, J., Selman, A., Culberson, J., & Reddy, P. H. (2022). Phosphorylated tau in Alzheimer's disease and other tauopathies. *International Journal of Molecular Sciences, 23*(21), 12841. https://doi.org/10.3390/ijms232112841

37. Resende, A. C., & Brand, C. (2022). Os impactos da neuroinflamação na doença de Alzheimer. *Clinical Biomedicine Research, 42*(4), 397-402. https://seer.ufrgs.br/index.php/hcpa/article/view/120200/88089. Acesso em 26/04/2024.

38. Ring, J., et al. (2022). The HSP40 chaperone Ydj1 drives amyloid beta 42 toxicity. *EMBO Molecular Medicine, 14*(5). https://doi.org/10.15252/emmm.202113952

39. Roda, A. R., Serra-Mir, G., Montoliu-Gaya, L., Tiessler, L., & Villegas, S. (2022). Amyloid-beta peptide and tau protein crosstalk in Alzheimer's disease. *Neural Regeneration Research, 17*(8), 1666-1674. https://doi.org/10.4103/1673-5374.332127

40. Saito, T., Chiku, T., Oka, M., Wada-Kakuda, S., Nobuhara, M., Oba, T., Shinno, K., Abe, S., Asada, A., Sumioka, A., Takashima, A., Miyasaka, T., & Ando, K. (2021). Disulfide bond formation in microtubule-associated tau protein promotes tau accumulation and toxicity in vivo. *Human Molecular Genetics, 30*(21), 1955–1967. https://doi.org/10.1093/hmg/ddab162

41. Sant'ana, N. J., et al. (2018). Terapia antiamiloide: uma nova estratégia para tratamento da doença de Alzheimer. *Revista Sociedade Brasileira de Clínica Médica, 16*(2), 127-131. http://www.sbcm.org.br/ojs3/index.php/rsbcm/article/view/347/315

42. Santos, J. M. S. C. (2016). *Imunomodulação no tratamento da doença de Alzheimer*. (35 f.). Tese (Doutorado) - Curso de Ciências Farmacêuticas, Universidade de Coimbra, Coimbra. https://estudogeral.uc.pt/bitstream/10316/48455/1/M_Joana%20Santos.pdf. Acesso em 17/07/2024

43. Savonenko, A. V., Wong, P. C., & Li, T. (2023). Alzheimer diseases. In J. M. Zigmond, C. A. Wiley, & M-F. Chesselle (Eds.), *Neurobiology of Brain Disorders* (2nd ed., pp. 313-336). https://doi.org/10.1016/B978-0-323-85654-6.00022-8

44. Schilling, L. P., et al. (2022). Diagnóstico da doença de Alzheimer: recomendações do Departamento Científico de Neurologia Cognitiva e do Envelhecimento da Academia Brasileira de Neurologia. *Dementia & Neuropsychologia, 16*(3), 25-39. https://doi.org/10.1590/1980-5764-DN-2022-S102PT

45. Sehar, U., Rawat, P., Reddy, A. P., Kopel, J., & Reddy, P. H. (2022). Amyloid beta in aging and Alzheimer's disease. *International Journal of Molecular Sciences, 23*(21), 12924. https://doi.org/10.3390/ijms232112924

46. Sereniki, A., & Vital, Frazão, M. A. B. (2008). A doença de Alzheimer: aspectos fisiopatológicos e farmacológicos. *Revista de Psiquiatria, 30*(1). https://www.scielo.br/j/rprs/a/LNQzKPVKxLSsjbTnBCps4XM/?format=pdf&lang=pt. Acesso em 26/04/2024

47. Silva, G. R. M., et al. (2020). Nursing: a study of the physiopathology of Alzheimer's and its alternative treatments with stem cells and cannabis. *Research, Society and Development, 9*(11), e39891110094. https://doi.org/10.33448/rsd-v9i11.10094. Acesso em 17/07/2024

48. Silva Neto, M. (2014). *Doença de Alzheimer: Imunoterapia contra Amiloide Beta*. (52 f.). Dissertação (Mestrado) - Curso de Ciências da Saúde, Universidade da Beira Interior, Covilhã. http://hdl.handle.net/10400.6/5023. Acesso em 17/07/2024

49. Sims, J. R., Zimmer, J. A., Evans, C. D., et al. (2023). Donanemab in early symptomatic Alzheimer disease: The TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA, 330*(6), 512–527. https://doi.org/10.1001/jama.2023.13239

50. Sousa, B. M. (2017). *Abordagem Terapêutica na Doença de Alzheimer*. (62 f.). Tese (Doutorado) - Curso de Ciências Farmacêuticas, Universidade de Algarve, Faro. http://hdl.handle.net/10400.1/10408. Acesso em 17/07/2024

51. Souza, E. S., Santos, A. M. S., & Silva, A. J. D. (2021). Doença de Alzheimer: Abordagem sobre a fisiopatologia. *Revista Epis Transversalis, 12*(2), 356-381. https://www.arca.fiocruz.br/bitstream/handle/icict/49903/AndrezaJB_silva_etal_IOC_2021.pdf?sequence=2&isAllowed=y. Acesso em 08/02/2024

52. Spillere, L. (2015). *Doença de Alzheimer: fisiopatologia e novas abordagens terapêuticas*. (47 f.). Monografia (Especialização) - Curso de Especialização de Farmacologia, Universidade do Extremo Sul Catarinense, Criciúma. http://repositorio.unesc.net/handle/1/3606. Acesso em 17/07/2024

53. Thoe, E. S., Fauzi, A., Tang, Y. Q., Chamyuang, S., & Chia, A. Y. Y. (2021). A review on advances of treatment modalities for Alzheimer's disease. *Life Sciences, 276*, 119129. https://doi.org/10.1016/j.lfs.2021.119129

54. Tuppo, E. H. A. B., Arias, A. S., & Hugo, R. (2005). The role of inflammation in Alzheimer's disease. *International Journal of Biochemistry & Cell Biology, 37*(2), 289-305. https://www.sciencedirect.com/science/article/abs/pii/S1357272504002699. Acesso em 14/04/2024

55. Vaz, M., & Silvestre, S. (2020). Alzheimer's disease: Recent treatment strategies. *European Journal of Pharmacology, 887*, 173554. https://doi.org/10.1016/j.ejphar.2020.173554

56. Ventura-Antunes, L., Nackenoff, A., Romero-Fernandez, W., Bosworth, A. M., Prusky, A., Wang, E., Carvajal-Tapia, C., Shostak, A., Harmsen, H., Mobley, B., Maldonado, J., Solopova, E., Snider, C., Merryman, W. D., Lippmann, E. S., & Schrag, M. (2024). Arteriolar degeneration and stiffness in cerebral amyloid angiopathy are linked to β-amyloid deposition and lysyl oxidase. *bioRxiv* [Preprint]. https://doi.org/10.1101/2024.03.08.583563

57. Wang, Y., et al. (2020). Modulation of neuroinflammation by cysteinyl leukotriene 1 and 2 receptors: implications for cerebral ischemia and neurodegenerative diseases. *Neurobiology of Aging, 87*, 1-10. https://www.sciencedirect.com/science/article/abs/pii/S0197458019304415?via%3Dihub. Acesso em 26/04/2024

58. Wegmann, S., Biernat, J., & Mandelkow, E. (2021). A current view on Tau protein phosphorylation in Alzheimer's disease. *Current Opinion in Neurobiology, 69*, 131-138. https://doi.org/10.1016/j.conb.2021.03.003

59. Yiannopoulou, K. G., & Papageorgiou, S. G. (2020). Current and future treatments in Alzheimer disease: An update. *Journal of Central Nervous System Disease, 12*, 1-12. https://doi.org/10.1177/1179573520907397

60. Zhang, Y., Chen, H., Li, R., et al. (2023). Amyloid β-based therapy for Alzheimer's disease: challenges, successes and future. *Signal Transduction and Targeted Therapy, 8*, 248. https://doi.org/10.1038/s41392-023-01484-7