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Chapter

Perspective Chapter: Alzheimer - A Complex Genetic Background

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Abstract

Alzheimer is a complex, multifactorial disease with an ever increasing impact in modern medicine. Research in this area has revealed a lot about the biological and environmental underpinnings of this disease, especially its correlation with B-Amyloid and Tau related mechanics; however, the precise biological pathways behind the disease are yet to be discovered. Recent studies evidenced how several mechanisms, including neuroinflammation, oxidative stress, autophagy failure and energy production impairments in the brain, –--- have been proposed to contribute to this pathology. In this section we will focus on the role of these molecular pathways and their potential link with Alzheimer Disease.

Keywords: molecular pathways, genetics, Alzheimer

1. Introduction

Alzheimer's disease (AD, MIM: 104300) is the most common neurodegenerative disorder worldwide, accounting for 60% up to 80% of Dementia causes [1]. This disease is one of the fastest rising diseases among the 50 leading causes affecting of life expectancy [2]; according to this trend, the number of AD subjects is destined to rise over 150 million by 2050 [3, 4].

AD worsen with time and as it progresses, patients usually develop short-term to long-term memory loss, accompanied by confusion, irritability and aggression, [5], followed by language impairments and mood swings [6].

Despite its prominence in modern society and the thriving research around it, a lot of its intricate pathophysiology is yet to be discovered. Furthermore, grade and type of symptoms may vary greatly from person to person [7], adding to the complexity of AD. Nevertheless, post mortem observations on AD subjects' Central Nervous System (CNS) evidenced some central histopathological features, mainly focused on amyloid beta (Aβ) plaques and neurofibrillary tangles (NFTs) [8–11].

Aβ plaques are the extracellular deposit of Aβ, which are produced by the cleavage of amyloid precursor protein (APP) [12], while the NFTs consist of abnormal filaments of hyper-phosphorylated Tau by GSK-3β [13]. They are thought to have a significant impact in memory and cognitive function, by triggering synaptic loss or dysfunction and neuronal death [14].

Interestingly, although not all of the causes have been located, AD cases seemingly converge to these hallmarks, providing a steady starting point for trying to understand the biological processes behind this disease.

1.1 Genetics

Indeed, among the cases of AD genetic studies individuated a form, known as Familial AD (FAD), that runs in families and is transmitted with an autosomic dominant model [15]. FAD is the best described type of AD: it is associated with mutations in three major genes: APP (chromosome 21), PSEN1 (chromosome 14) and PSEN2 (chromosome 1) [16]. Alterations within these genes affect amyloid

Familial AD (FAD)	**OMIM ID**
An Alzheimer's disease that has_material_basis_in mutation in the gene encoding the amyloid precursor protein on chromosome 21q.	OMIM:104300
An Alzheimer's disease that has_material_basis_in mutation in the presenilin-1 gene (PSEN1) on chromosome 14q24.	OMIM:607822
An Alzheimer's disease that has_material_basis_in a mutation in the presenilin-2 gene (PSEN2) on chromosome 1q42.	OMIM:606889
Sporadic AD (SAD)	
An Alzheimer's disease that is characterized by an association of the apolipoprotein E E4 allele.	OMIM:104310
An Alzheimer's disease that is characterized by an associated with variation in the region 12p11.23-q13.12.	OMIM:602096
An Alzheimer's disease that is characterized by an associated with variation in the region 10q24.	OMIM:605526
An Alzheimer's disease that is characterized by an associated with variation in the region 10p13.	OMIM:606187
An Alzheimer's disease that is characterized by an associated with variation in the region 20p12.2-q11.21.	OMIM:607116
An Alzheimer's disease that has_material_basis_in heterozygous mutation in ABCA7 on chromosome 19p13.3.	OMIM:608907
An Alzheimer's disease that is characterized by an associated with variation in the region 7q36.	OMIM:609636
An Alzheimer's disease that is characterized by an associated with variation in the region 9p22.1.	OMIM:609790
An Alzheimer's disease that is characterized by an associated with variation in the region 8p12-q22.	OMIM:611073
An Alzheimer's disease that is characterized by an associated with variation in the region 1q21.	OMIM:611152
An Alzheimer's disease that is characterized by an associated with variation in the region 1q25.	OMIM:611154
An Alzheimer's disease that is characterized by an associated with variations in the region 3q22-q24.	OMIM:604154
An Alzheimer's disease that is characterized by an associated with a risk allele in in the PCDH11X gene on chromosome Xq21.3.	OMIM:300756
An Alzheimer's disease that is characterized by an associated with mutations in the gene TREM2.	OMIM:615080
An Alzheimer's disease that has_material_basis_in a mutation in the ADAM10 gene on chromosome 15q21.	OMIM:615590
An Alzheimer's disease that is characterized by associated variants of the gene PLD3.	OMIM:615711

Table 1.
Alzheimer sub-types according to genetics [30407550].

cleavage, directly promoting plaques formation. Several studies demonstrated that alterations in APP or PSEN1 genes are guaranteed to cause AD, while PSEN2 mutations have a 95 percent chance of causing the disease [17]. Unfortunately, only up to 5% of all AD cases are of this type [18].

Other cases usually go under the name of sporadic AD (SAD) which encloses the largest part of AD cases. SAD cases have a more cryptic and heterogenic genetic background [18]: More than 500 candidate genes were correlated with SAD [15, 19, 20]. Of them, inherited polymorphic APOe (chromosome 19) E4 allele is the major risk factor. APOe is the gene encoding for the Apolipoprotein E, whose function is to bind lipids and sterols and transport them through the lymphatic and circulatory systems. APOe4 is thought to produce a more instable form and is related to the formation of neurofibrillary tangles [21, 22] and amyloid clearance processes [23, 24], through a still not well understood mechanism.

1.1.1 Apolipoprotein E (APOe)

APOe is in charge of cholesterol transport in the brain [25, 26]. As said before, the e4 isoform of this protein is associated to increased AD-risk [27–30]. The fine molecular mechanisms behind the risk increase operated by APOe4 are not completely characterized, however data obtained from cell cultures evidenced how APOe4 promotes oxidative stress and the generation of neurotoxic fragments which impairs mitochondrial activity [31–33]. In particular, APOe4 isoform seems correlated to an increased α-synuclein (αSyn) accumulation accompanied with synaptic loss, lipid droplet accumulation and dysregulation of intracellular organelles [34]. αSyn is a presynaptic membrane-bound protein abundantly expressed in the brain and is involved in synaptic signaling and membrane trafficking [34]. Further, over other 50 loci/genes have been implicated in SAD [15, 35, 36], underlining AD's complexity and the possibility of it being triggered by different alterations. Indeed, up to date, literature (OMIM and GO) reports 19 different AD subtypes based on different associated loci. **Table 1** reports a summary of such subtypes.

2. The pathways of Alzheimer disease

The number of genetic factors described is important contributors to AD. However, neither APOE4 nor the other correlated genes are entirely sufficient to explain (and promote) the totality of AD cases [37].

In such a complex environment represented by multicellular organisms a gene and its product/s is not a stand-alone entity. Each protein interacts with and influences many other elements in a synergic orchestra that regulates an organism.

As such, a single alteration propagates (indirectly) its effects to its interactors following pathways and molecular cascades.

Indeed, rather than single genes, a better approach would be investigating AD as an event related to alterations affecting entire biological pathways. Within this chapter, we will focus on molecular cascades potentially involved in AD. A plethora of mechanisms, including neuroinflammation [38], oxidative stress [39, 40], defects in mitochondrial dynamics and function [41], synaptic and cholinergic malfunctions [42], cholesterol and fatty acid metabolism as well as glucose energetic pathways impairments in the brain [43, 44], autophagy failure [45], apoptosis with multiple cell signaling cascades [42, 46] and other less studied mechanisms have been proposed to contribute to AD. It should be stressed that while they are discussed separately, these pathways are all interlinked and changes in one may very well result in changes in the others.

2.1 Hallmarks of AD: Aβ and tau related pathways

Aβ is 4 kDa fragment derived by two subsequent proteolytic cleavages of amyloid precursor protein (APP) by β and γ secretases [47]. As evidenced in studies focused on FAD, genetic alterations of APP, PSEN1 and PSEN2 may negatively influence cleavage promoting Aβ production. Interestingly, contrary to what was once believed, low concentrations of Aβ are seemingly needed to short and long term memory processes [48, 49], and Aβ homeostasis is a lot finer regulated process than once expected, consisting of highly conserved feedback loops and interactions between multiple processes [50].

Potentially risk genes may be found among the ones regulating the biological networks involved in Aβ expression and APP cleavage (including APP, PSEN1, PSEN2, ADAM10, BACE1), its localization and transport (like APOE, CLU, SORL1) and its degradation and clearance (including ABCA7, BIN1, CD2AP, CD33, PICALM, PTK2B and RIN3) [50, 51]. Interestingly, the same elements are interlinked with other important pathways (see later in the text). Aβ accumulation also impairs the structure and function of microglia, astrocytes, and vascular endothelial cells of the brain [52, 53].

The neurotoxic function of Aβ is linked to Tau, a microtubule-associated protein that provides structural assembly and stability of cytoskeletons [54, 55]. The expression of tau is critical during Aβ-mediated synaptotoxic processes where Aβ peptides target phosphorylation-based pathways [55] which hyper-phosphorylate Tau protein through glycogen synthase kinase 3 beta (GSK-3β) and other kinases activated by Aβ peptides [56], and promote their release from microtubules. The removal of Tau from microtubules favors the formation of NFTs composed by aberrantly folded form of hyper-phosphorylated tau and alter the structure of neuritis, giving rise to synaptic malfunction and neuronal death [52].

2.2 Oxidative stress

Oxidative stress (OS) has been widely recognized as a prodromal factor associated to AD [57]. According to the current knowledge, increased OS is a sign often observed in the brain of early-stage AD subjects [58]. In particular, OS may act as indicator of changes within the brain. Regarding its correlation with Aβ accumulation, it is known that Aβ is both a cause and the result of OS, as Aβ structure facilitates OS induction [59] and represents a source of radical oxygen and nitrogen species (ROS, RNS) [57]. Through proteic mediators, including NOX, TGF-β, NF-κB and NRF2 genes 'products [60], Aβ increases OS levels and triggers several molecular events that are strictly linked with AD development [61]: OS promotes Tau phosphorylation [62] and also exerts its effect on the choline recycling from the synapse processes, leading to ACh deficiency [63]. It also causes deficit in the energy metabolism (through impairment of mitochondria function and Blood Brain Barrier (BBB) permeability) and leads to apoptosis and then neurodegeneration [64–66]. Of particular relevance, excessive ROS inevitably lead to lipid peroxidation [67], which has been proposed as early biomarker of AD [68]. OS cause damage to all biomolecules. In particular, unsaturated lipids are very sensitive to their action. It should be noted that the brain gray matter and white matter are both very rich in polyunsaturated fatty acids (e.g. docosahexanoic acid, adreinic acid which are brain tissue specific) [69], making the nervous system very sensible to lipid peroxidation [69]. The action of OS in AD through lipid peroxidation is supported by histological evidences showing the co-localization of lipid peroxidation metabolites and Aβ plaques in the brain [70]. Further, it was demonstrated (in culture studies)

that the lipids usually found in AD brain lesions produce neurotoxic effects in presence of increased OS levels [71]. Indeed, the chemical reactions following lipid peroxidation often results in the production of isoprostanes and malondialdehyde, which causes DNA damage and toxic stress in cells [72]. Interestingly, the products of lipids peroxidation can be found in bio-fluids such as blood and urines, supporting their potential for diagnosis of AD. As AD potential biomarkers, some of these metabolites were investigated in literature [73]. However, their effective use in clinic is still debated as they showed some promising but contradictory results [68].

2.3 Inflammation

Inflammation is a physiological acute event, which is essential to defend the body against toxins and pathogens and for tissue repair. However, if inflammation becomes chronic, it causes detrimental effects with severe consequences. Among the processes involved with AD, the persistent over-activation of the inflammatory cascade represents one of the main biological mechanisms through which AD progresses: indeed, neuroinflammation is not typically associated to AD onset, but it plays a key role in increasing the severity of the disease by exacerbating Aβ and Tau nefarious effects [74–76].

The main players behind cytokines production are the non-neuronal cells that populate the brain, such as microglia, astrocytes, and oligodendrocytes [77–79].

Literature data evidenced that Aβ up-regulates cytokines production by these cells. Further, the presence of Aβ stimulate microglia toward the chronicization of pro-inflammatory state by activating the NF-κB cascade [80–82] or promoting Aβ interaction with FPR2 [83]. Under such conditions, microglia generates a wide range of cytotoxic factors, including interleukins, TNF-α, superoxide, nitric oxide, ROS, prostaglandins and Cathepsin B, which damage extracellular matrix and cause neuronal dysfunction [75, 84]. The increase of cytokines triggers several potentially harmful effects: it induces mitochondrial stress in neurons, either directly or indirectly, including via Aβ signaling. It also increases OS [85, 86] and Blood–Brain Barrier (BBB) permeability which likely influence AD progression [87].

Similar to microglia, astrocytes also produce and/or release an array of inflammatory mediators. Activated or "reactive" astrocytes can be roughly classified in two groups: the "A1" neurotoxic phenotype and the "A2" neuroprotective phenotype based on distinct transcriptional profiles [88]. The A1 group is likely involved with AD through mechanisms similar to microglia.

From a molecular point of view, cytokines like IL-1 and TNF-α promote Aβ production by up-regulating APP and the amyloidogenic secretases [81, 89], while IL-6 and IL-18 promote Tau hyper-phosphorylation [90, 91].

Ultimately, a cycle is established in which inflammation increases Aβ production (and triggers other negative processes increasing protein accumulation and OS), which in turn stimulate microglia to maintain its pro-inflammatory state. The uncontrolled cytokines production then causes neuronal death [38] as it damages synapses (please refer to Section 2.4), myelin sheaths and axons, promote complement-mediated damage and/or triggers apoptotic or necroptotic mechanisms [92]. This link between AD and microglia is also supported by Genome wide association studies, which evidenced how several genes (TREM2, CLU, CR1, EPHA1, ABCA7, MS4A4A/MS4A6E, CD33, CD2AP) related with an increased AD risk regulate glial inflammatory reaction [75]. Additionally, it has been observed that astrocyte-based inflammatory cascade could recruit peripheral macrophages, white blood cells, and lymphocytes that infiltrate brain parenchyma thanks to BBB increased permeability and vascular alterations [93].

2.4 Neurodevelopment and neurotransmission associated processes

Neurodevelopmental/Neuroplasticity and Neurotransmission related pathways are likely associated with AD development and in particular with its cognitive symptoms [94]. Physiologically, these processes consist in the proliferation, differentiation and maturation of neural stem cells (NSC) and the modulation of their interactions through synapse- and neurotransmission- related processes.

Regarding neurodevelopment processes, it has been observed that the synaptic pruning pathway becomes aberrantly up regulated in the first stages of AD. This aberrant activation, which leads to synaptic loss [95], seems to be triggered by Aβ, through PANX1, ryanodine receptor (RyR) function [96, 97] other than several inflammatory signals [98].

PANX1 is a protein involved in the modulation of neurotransmission, neurogenesis and synaptic plasticity [99]. An increase of this protein under inflammatory conditions contributes to neuronal death [100].

RyR is Ca2+ channel which modulates different processes including neuronal development and plasticity [101].

The anomalous RyR channel function is triggered by Aβ and OS through Ca2+ increased concentrations [96] and are interlinked to mitochondrial and NOX2-mediated ROS generation [102] and glial activation [103].

Regarding the inflammatory elements, it has been observed that many cytokines directly interact with receptors located on neuronal membranes. Here they activate or modulate pathways involved in synaptic function and plasticity (e.g. p38 MAPK and NFκB pathways). Further, synapse function and stability are also heavily regulated by microglia and astrocytes. In particular, the former is seemingly implicated in pruning mechanics [95], while the latter appear to have an heavy involvement in regulating synapse formation, stability, and turnover [104]. Astrocytes physically wrap synapses. The synapse/astrocyte interface is fairly active as astrocytes release numerous proteins capable of modulating synaptic function, sprouting and remodeling.

Regarding neurotransmission, several reports have indicated a significant reduction of Serotonin (5-HT) [105], Dopamine (DA) [106] and Norepinephrine (NE) [107] levels as well as their receptors in AD brain. In AD, loss of 5-HT results in depression, anxiety and agitation [108], dysregulation of DA release leads to reward-mediated memory formation deficits [109] and low level of NE impairs spatial memory function [110]. Glutamatergic and cholinergic abnormalities in particular, were pointed as one of the principal causes of cognitive deterioration in AD.

2.4.1 Cholinergic neurotransmission

The cholinergic system regulates attention processing [111], cognition [111], memory function and behavior via the release of the neurotransmitter acetylcholine (ACh) [112].

Several studies evidenced how ACh production and reuptake are impaired in AD brains [113]. Further, accumulation of intraneuronal Aβ degenerates basal forebrain cholinergic neurons and reduces ACh levels [114], which in turn leads to memory deficits [115]. A potential candidate through which Aβ exerts its effect is α7nAChRs. Studies on α7nAChRs KO models evidenced how the lack of this receptor could induce AD-like pathology, including Aβ increase. In addition, its depletion is linked to an increased age-dependent expression of phosphorylated Tau [116, 117].

About the mechanisms underlying α7nAChR regulation of Aβ production, it seems that physiologically this receptor activations shifts APP processing toward

the non-amyloidogenic pathway [118], enhancing the production of the neuroprotective APPα (soluble form) which is able to counteract Aβ neurotoxicity [119]. Interestingly, α7nAChRs mediate the intake of pre-synaptic Ca2+ levels during neuronal activity, indirectly modulating all biological processes dependent on this ion, glutamate release, synaptic transmission, and cognitive function [120]. When α7nAChRs is reduced, a negative feedback mechanism is triggered which increase Aβ production with the aim of maintaining Ca2+ influx in the cells [121]. Aβ in turn, further decrease its expression. This reduction ultimately exerts its effect on the N-methyl-D-aspartate receptor (NMDAR), which is removed from membrane, and on nicotinic and MAPK signaling, resulting in the development of cognitive deficits [122].

2.4.2 Glutamatergic neurotransmission

The most common excitatory neurotransmitter, glutamate, and its receptors are required for neuronal cell differentiation, migration, survival, and synaptic plasticity. There are two types of glutamate receptors: ionotropic glutamate receptors (iGluRs), such as N-methyl-D-aspartate (NMDA), α-Ammino-3-idrossi-5-Metil-4-isossazol-Propionic Acid (AMPA) and Kainate receptors; and metabotropic glutamate receptors (mGluRs).

Over-activation of these receptors causes neuronal excitotoxicity as well as neuronal death, and this is thought to be one of the mechanism causing neurodegeneration in AD [123]. Indeed, in patients with AD, available evidence points to a disruption in the glutamatergic neurotransmission cycle at the point of glial cell reuptake of free glutamate from the synapse: Aβ can interfere with glutamate receptors and transporters [96]. The binding of such receptors triggers neuronal susceptibility to glutamate excitotoxicity, dyshomeostasis and defective plasticity [124]. The biological mechanism is still not well understood, but likely needs the function of a tyrosine-protein kinase, Fyn, which alter NMDARs function through phosphorylation [125]. Interestingly, Astrocytes may also play a role in the impaired glutamate clearance from the synaptic cleft. As said before, astrocytes wrap synapses. In the synaptic interface, these cells present a high concentration of excitatory amino acid transporters (EAATs), including EAAT1 and EAAT2. Physiologically, over 80% of extracellular glutamate is taken by astrocytes through these transportes [126]. It has been observed that Aβ peptides and pro-inflammatory elements down regulate the expression of EAATs, impairing glutamate clearance [127]. As such, free glutamate accumulates out of synapses while the vesicular glutamate uptake is reduced. The consequence of this condition is a chronic low-level activation of glutamatergic receptors on postsynaptic neurons and reduced sensibility to glutamate during neuronal firing (due to the low concentration of the neurotransmitter within vesicles) [128], leading to suboptimal neurotransmission and impairment of long-term potentiation (LTP) [128].

2.5 Energy metabolism

Energy is of high importance to maintain the physiological function of the brain. Processes related to energy production (Glucose intake, ATP production) are disrupted in AD brains [129]: Indeed, several brain areas in AD patients show a significant decrease of glucose metabolism [130]. Additionally, the first AD-related intracellular lesions usually develop in neurons with a higher energy consumption [131] and often involve enzymes related to tricarboxylic acid cycle, which lead neurons to a hypo-metabolic state [63].

Interestingly, an excess of an important energy substrate, glucose, may also lead to the exacerbation of AD symptomatology. A high glucose concentration is also the main characteristic of diabetes. Other than being a risk factor for the development of diabetic complications, it seems to play a role in the development of AD cognitive symptoms [132].

Indeed, high levels of glucose are harmful for the brain, as they lead to Aβ accumulation on brain lesions. It also exacerbates OS and promotes neuroinflammation [133, 134], with the consequences already described in the previous sections.

Glucose levels are affected by numerous elements, such as pro-inflammatory cytokines [135, 136]. However, the main control is exerted by the antagonistic function of insulin and glucagon.

Insulin signaling has been the focus of multiple AD studies [137–139] were it was shown that both Aβ deposition and tau hyperphosphorylation are correlated with the impairment of Insulin signaling cascade [140, 141], and insulin resistance in particular.

According to these observations, insulin resistance is a feature of both type 2 diabetes mellitus (T2DM) and AD, supporting a biological overlapping between the two pathologies. As said before, the high glucose condition increases Aβ production. On a molecular level this increase is linked to the inhibition of APP degradation pathways [142].

Chronic hyperinsulinemia in brain also leads to cognitive dysfunctions [143], Insulin receptor is present in hippocampus [144], the main area responsible for memory. A chronic exposition to insulin favors a resistance mechanism, making neurons less responsive to this hormone. Further, Aβ can interact with insulin receptors causing their internalization and thus inhibiting their function [145]. Additionally, Aβ seizing insulin receptor, increases insulin levels in the brain microenvironment, which in turn promote inflammation increasing TNFα, interleukin 1β and 6 (IL1β and IL6) [146].

Through a still not completely understood mechanic, the alteration of insulin signaling (or an increased resistance to insulin) ultimately triggers neuroinflammation and neurodegeneration, increasing Aβ concentrations and Tau hyperphosphorylation [145, 147].

2.6 Autophagy impairments

Autophagy is an intracellular process mediated by vesicles and lysosomes that consists of several sequential steps which ultimately lead to the degradation of damaged/misfolded proteins and dysfunctional organelles, thereby sustaining cellular homeostasis [148].

Physiologically, this process is especially important for neuronal and glial cells health [149, 150]. Although it is still not clear whether dysfunction of autophagy is the cause or result of AD [151], it has been observed that the dysregulation of autophagy may occur in early stage of the disease. In particular, this process is believed to be a major pathway for Aβ clearance/accumulation [152] and is also involved in the pathological mechanisms of neurodegeneration [149, 150]. Studies on animal models also reported that restoring the physiological autophagosomes clearance ameliorate/prevents AD cognitive symptoms [153].

Studies on AD brains revealed a significantly higher presence of autophagosomal and pre-lysosomal vacuoles in neuronal dendrites and axons [154–156]. These vacuoles were shown to be enriched in APP, γ-secretase components, PSEN1 and nicastrin, which are required to generate Aβ [157, 158]. According to the autophagic hypothesis, the block of autophagy and the consequent accumulation of autophagosomes trigger neuronal degeneration [156] and leads to the release of these vesicles

in the extracellular space where they form the characteristic AD plaques [159, 160]. Autophagy is also essential for Tau clearance [161]. Usually, Tau is transported in vacuole for degradation, however certain mutations of Tau, cause the block of this protein in the membrane of lysosome. The accumulation in the membrane impairs and disrupts lysosomes function and structure, which ultimately lead to the release of lysosomal enzymes in the cytoplasm [161].

Recent studies have proven that autophagy could be influenced by diverse factors, such as Aβ [162] and OS [163]. In addition, ApoE4 and Aβ influence of lysosomal membranes stability [164].

From a biological point of view, autophagy is mainly regulated according to the physiological condition of cells through several elements:

ATG7 is a key gene regulating autophagy process [150]. It is involved in degradation of tau [165] and mediates the transport of Aβ peptides [166]. Alterations of its function have been correlated with AD [167].

Beclin 1 (*BECN1/ATG6*) protein mediates the initiation of autophagy [150]. BECN1 is involved in the pathophysiology of AD. The expression of BECN1 is decreased in brains of AD patients when compared with healthy individuals [168]. Decreasing of Becn1 expression leads to increased levels of Aβ [168] and also increases microglia inflammatory response [169].

The down-regulation of this protein is believed to be caused by caspase-3 up-regulation [170]. Further, BCL2 Apoptosis Regulator (BCL2) is an anti-apoptotic factor that regulate autophagy through BECN1 [171]. The overexpression of Bcl2 has protective effects against Aβ-driven neuronal death [170]. The overexpression of Bcl2 affects also tau processing, reducing the number of NFTs [170].

Cyclin Dependent Kinase 5 (CDK5) is an autophagy-regulating kinase [150], which influences the metabolism and effects of Aβ. CDK5 likely act through regulation of β-secretase, which is a crucial enzyme involved in APP metabolism [172]. This kinase also mediates Aβ peptide-induced dendritic spine loss [173], providing a pathway linking Aβ with cognitive dysfunction. Similarly, CDK5 is similarly involved in tau phosphorylation [174], although it seems to not be sufficient to trigger NFT formation [174].

Clusterin (*CLU/APOJ)* is a chaperone protein implicated in autophagosomes biogenesis via interaction with ATG8E (MAP1LC3A) [150]. According to meta-analyses data on AD subjects, *this protein is* one of the top AD candidate genes [37, 175, 176]. Its alterations have been suggested to affect neuron connectivity in several brain regions [177, 178]. Physiologically, CLU interacts with Aβ, preventing its aggregation [179, 180].

Cathepsin D (*CTSD*) is a lysosomal protease [150] involved in APP and Aβ degradation [181]. Its role and correlation in AD is still under debate as literature produced controversial results [182–185].

Alpha-Synuclein (*SNCA/PARK1/NACP*) is another protein found to be associated with AD risk [150]. SNCA is an important component of Aβ plaques [186] and can influence the expression of/be regulated by Aβ peptides [187, 188]. Similarly, to interaction of SNCA with Aβ peptides, SNCA and tau also induce each other fibrillization [189]. SNCA binds, phosphorylates, and inhibits microtubule assembly activity of tau [190].

PINK1 and PRKN genes products are important elements behind autophagosome-mediated mitochondrial degradation [191]. In AD, high levels of Aβ inhibit the expression of those proteins, leading to increased dysfunctional lysosomes and neurodegeneration [192, 193].

Ubiquilin 1 (*UBQLN1*) is involved in autophagosome–lysosome fusion [150], likely through ATG8E (MAP1LC3A) [194]. Meta-analyses *studies correlate UBQLN1* with an increased risk for AD [195, 196]. It has been observed that the

expression of UBQLN1 is reduced in AD patients [197, 198]. This decrease, in turn, up-regulates APP processing [198].

Ubiquitin C-Terminal Hydrolase L1 (*UCHL1*) influences autophagy by interaction with LAMP2 which modulates autophagosome-lysosome fusion [150]. Uchl1 interacts with App [199]. Its over expression decreases Aβ and NFT production [199] and lower levels of UCHL1 have been found in AD patients [200]. Regarding its autophagic role, it has been observed that UCHL1 is involved in lysosomal degradation of BACE1 [200].

Of all the described autophagic regulators potentially linked with AD, the mammalian target of rapamycin (mTOR) has been studied most investigated and is considered to play a key role in autophagy biogenesis. The mTOR protein acts as inhibitor in autophagy regulation through different pathways, including AMPK and PI3-Akt [201, 202]. In neurons and glial cells, mTOR is highly expressed an play an important role for synaptic plasticity and memory [202]. In neurons and glial cells, mTOR proteins are highly expressed, and their modulatory activities are fundamental in brain development. In the adult brain, mTOR signaling plays a crucial role in the translational initiation of protein synthesis required for synaptic plasticity and memory formation. However, uncontrolled mTOR activity leads to impairment of such processes. Numerous studies on AD brains and AD mice models revealed mTOR hyper-activation in AD brain [203]: Aβ accumulation seems to promote the activation mTOR pathway through phosphorylation of the mTOR inhibitor PRAS40 [204]. Further, hypo-energetic states may also activate mTOR [146].

Interestingly, a defective autophagy in other cells, including Astrocytes, microglia, and oligodendrocytes has also been linked to AD. In particular, disturbing basal autophagy processes in glia trigger neuroinflammation, which, as previously described, is an important pathway leading to the progression of AD [205].

2.7 Cerebrovascular abnormalities

In patients with AD, cerebrovascular abnormalities are a common comorbidity [206, 207]. These may contribute to the onset of cognitive impairment and dementia. Altered cerebral blood flow and pressure at the level of the brain are induced vascular dysfunction [208]. These events are injurious to normal brain function that would result in disturbed homeostasis, but also in blood–brain barrier (BBB) damage and micro-fractures in cerebral vases [209]. It has also been observed that the permeability of BBB to immune cells and molecules increases with aging. As said in the previous sections, the infiltration of immune cells in the brain parenchyma favors neuroinflammation [210] and ROS production [206], thus increasing the risk of AD [81].

These events are linked to the formation of Aβ plaques [211]. In particular, ROS production is related to the increase of the Advanced Glycation Endproducts (AGE) proteins and their receptors (RAGE) in the vascular system [212, 213]. A chronic hypo-perfusion state favors the formation of Aβ through the activation of the adaptive response to hypoxia and reduced clearance via perivascular draining [214, 215]. Furthermore, Aβ accumulation seems to be mainly localized in brain areas with reduced cerebral blood flow [216]. Finally, as said before, AD brains are in a pro-inflammatory state; in these conditions Notch signaling is up regulated [217]. Notch signaling has an essential role in vascular development and angiogenesis in brain through the modulation of VEGFR2 [218]. It has been observed that chronic activation of Notch1 negatively affect the brain microenvironment, in particular the delicate connection of the brain with cardiovascular system. Indeed, Notch signaling, in association with VEGF, has been demonstrated to cause impaired blood flow, further reducing the nutrients intake by neurons (worsening the already weak energetic

state). Notch also induces BBB leakages, which has severe impact on the brain and may accelerate Aβ accumulation [217]. BBB homeostasis also depends on the role of astrocytes as the act as bridge between the vascular and neuronal compartment. Several studies have observed that astrocytes go through morphological changes in proximity of vascular Aβ deposits [219]. These alterations likely occur during early stages of the disease and evidence a neurovascular uncoupling, which ultimately lead to a dysfunction of BBB barrier. It has been observed that the alteration of astrocytes induces an age-dependent accumulation of amyloid [220].

2.8 Signal transduction

2.8.1 Alteration in PKC signaling

Protein kinase C (PKC) family in mammalian is divided in three subfamily: a) calcium-dependent PKC (cPKC), necessity of DAG and Ca^{2+} presence for triggering; b) calcium-independent isoforms (nPKC), that requires DAG presence; c) an atypical isoform of PKC (aPKC) [221]. PKC isoforms are involved in several neural processes, including the ones related to cognitive function. The cPKC and nPKC isoforms could have impact on synaptic formation and plasticity, spatial memory organization or dendritic loss [221], while aPKC isoform is involved in long-term memory [222]. A deficiency in PKC isoforms signaling is thought to be involved in AD [223]. Indeed, deficiency of bPKC is correlated with Tau hyper-phosphorylation (through GSK-3b) while lack cPKC and nPKC activation down-regulates α-secretase activity [222, 224]. Furthermore, Aβ contributes to inhibit PKC isozymes [223, 224].

2.8.2 Wnt signaling pathway

The Wnt signaling pathways play a crucial role in the central nervous system during all phases of neuronal growth and development and remain significant in the adult nervous system [225]. In adults, this process is particularly important since it manages memory creation, maintenance, and behavior. Alteration of this process is strongly linked to neurodegeneration [225]. Altered function of Wnt signaling components was detected in AD brain, including down regulation of b-catenin translocation into the nucleus [226]. The reduction of b-catenin in neurons nuclei triggers the overexpression of the Wnt antagonist GSK-3b and Dkk-1 [225, 227]. GSK-3b, as discussed before, is the main enzyme in charge of tau hyper-phosphorylation. Furthermore, it participates in OS generation, which ultimately disrupts neuronal function [227].

2.8.3 Calcium role

Cellular Ca^{2+} is a key ion involved in the regulation several processes in neurons [228, 229]. Its dyshomeostasis may play a key role in the pathogenesis of AD [230] and may even precede the formation of Aβ plaques and NFTs [228].

Intracellular Ca^{2+} is usually stored in the Endoplasmatic Reticulum. Its release in the cytosol is finely controlled by multiple pathways, including RyRs and inositol 1,4,5-trisphosphate receptors (InsP3R) -related ones [231]. Even its intake from the extracellular environment is tightly regulated by multiple processes, such as the store-operated Ca2+ entry (SOCE) pathway and the voltage-gated Ca^{2+} channels (VGCC) [232].

As discussed before in the neurotransmission section, the physiological Ca^{2+} influx stimulates the processing of APP by α-secretase [230], thus protecting from Aβ accumulation. Imbalanced cellular Ca^{2+} contributes to pathophysiological

conditions such as accumulation of Aβ plaques and neurofibrillary tangles, protein misfolding, necrosis, apoptosis, autophagy deficits, and degeneration [230, 233].

Finally, excess cytosolic Ca^{2+} concur in mitochondria dysfunction and dysregulates KIF5-Miro-Trak-mediated mitochondrial transport to synapses [63].

High OS states and the presence of Aβ can interfere with Ca^{2+} homeostasis, releasing it from ER stores through the InsP3R and RyR [230, 234]. In addition, the increased intracellular Ca^{2+} levels in the cells interfere with the physiological function of VGCCs, thus impairing neurotransmission [230, 233].

2.9 Balance of phosphorylation: Kinases and phosphatases

Protein phosphorylation and dephosphorylation are two essential cellular mechanisms through which a wide-range of receptors and trasduction cascades are regulated. Numerous kinases and phosphatases are encoded in our genome; these two class of enzymes works balancing each other, maintaining an equilibrium phosphorylation and dephosphorylation. Impairment of such finely regulated process has been correlated with AD. As said before in this chapter, one of the trademarks of AD is the hyperphosphorylation of Tau protein, which triggers in a prion-like manner the formation of NFTs. It has been observed that Tau protein has over 85 potential phosphorylation sites [235].

There are several protein kinases that could phosphorylate Tau [236], some of them involved in the pathways discussed so far, including gsk-3β, cdk5, microtubule affinity regulated kinases (mark), tau-tubulin kinases (ttbk), Tyrosine-protein kinase Fyn (Fyn) or Tyrosine-protein kinase Abl1 (Abl1), protein kinase A (pka), Calcium/calmodulin-dependent protein kinase (CaMKII) [236, 237]. All of these kinases have been correlated with an increased risk of AD and are capable of phosphorylate tau at multiple sites [237]. In particular, it appears that phosphorylation of Thr231 and Ser262 residues are critical for NFTs formation.

Hyperphosphorylation of Tau can also be reached and maintained through inhibition of phosphatases. Protein phosphatase 2A (PP2A) is the major enzyme that accounts for ~71% of the total tau dephosphorylation activity [238]. This enzyme co-localizes with tau and microtubules in the brain [239]. In AD, the activity of PP2A is decreased [240]. Interestingly, its down-regulation not only decrease the dephosphorylating activity but also activates CaM-KII and PKA pathways, favoring hyperphosphorylation, as it has been observed in some in vitro and in vivo studies [241, 242].

Other phosphatases have also a role in AD, including Striatal-Enriched protein tyrosine Phosphatase is an intracellular phosphatase (STEP), protein phosphatase 1 (PP1), protein phosphatase 5 (PP5), Calcineurin (PP2B), PP2C [243], through complex feedback mechanisms.

In particular, recent evidences pointed to STEP as one of the targets via which Aβ exerts its deleterious effects in AD. Elevated levels of Aβ seems to be involved in the activation of Step through the activation of α7nAChRs [244, 245] and the subsequent increase of calcium influx [245]. This triggers a cascade of molecular events (in which PP2B and PP1 are also involved) that ultimately activate STEP. STEP mediates the Aβ-induced cognitive impairment by dephosphorylation of important elements involved in synaptic plasticity and dendritic density (such as SPIN90, PSD-95 and Shank), eventually causing the collapse of synapses [246, 247].

Interestingly, the regulation of kinases and phosphatases is strictly linked to glucose metabolism, through the protein kinase AMPK (Ampk). Moreover, Aβ transiently inhibit AMPK potentially providing a link between Aβ and metabolic defects in the AD brain [248]. The activation of AMPK is correlated with glucose metabolism and is related to gluconeogenesis, IR and insulin deficiency. AMPK mediates

phosphorylation and signal transduction through GSK-3β [249], PP2A [250], beta-secretase 1 (BACE1) and sirtuin1 (SIRT1). In addition, through SIRT1, AMPK promotes autophagy. Physiologically AMPK cascade inhibits hyperphosphorylation of tau and can reduce Aβ production. Impairments of this cascade potentially lead to AD progression.

3. Conclusions

AD is one of the main causes of disability and decreased quality of life worldwide. Despite the ever-increasing number of studies, many fundamental questions remain regarding the molecular background of this disease.

The evidences derived from the recent data on AD stress its "multifactorial nature" and clearly indicate the necessity to consider wider approaches while trying to understand its biological mechanics. This chapter wanted to contribute toward and stress this new 'pathway-like' perspective on AD. A much deeper discussion would be needed to explore the cascades potentially linked with the disease and surely, a lot is still to be discovered. Research activity in this area is very fervid a new data is accumulating daily in the scientific community. As a final but very important note, our genes and pathways (altered or not) do respond, interacts and adapt 'continuously' to external stimuli. Although they were not discussed here, these environmental factors should always be considered as they can greatly influence the biological mechanisms behind multifactorial pathologies such as AD [1, 251]. Further, Epigenetic dysregulation also seems to be involved in AD as methylation mechanics [252, 253] and miRNAs signaling [254] have been found to be altered in AD brain. The key to further deepen the studies of AD would be to understand how all these processes interact and influence with each other and act in concert toward this disease progression.

Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

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Nomenclature

5-HT	Serotonin
ABCA7	ATP Binding Cassette Subfamily A Member 7
ACh	Acetylcholine
AD	Alzheimer's disease
ADAM10	ADAM Metallopeptidase Domain 10
AGE	Advanced Glycation Endproducts
AMPA	α-Ammino-3-idrossi-5-Metil-4-isossazol-Propionic Acid
AMPK	5′ adenosine monophosphate-activated protein kinase
aPKC	atypical isoform of PKC
APOe	Apolipoprotein E gene

APP	Amyloid precursor protein
Aβ	Amyloid beta
BACE1	Beta-Secretase 1
BBB	Blood Brain Barrier
BIN1	Bridging Integrator 1
CD2AP	CD2 Associated Protein
CD33	CD33 Molecule
CLU	Clusterin
CNS	Central Nervous System
cPKC	calcium-dipendent PKC
DA	Dopamine
DAG	diacylglycerol
DKK1	Dickkopf-1
ER	Endoplasmatic Reticulum
FAD	Familiar AD
FPR2	formyl peptide receptor type 2
GBA	
GSK-3b	glycogen synthase kinase 3 beta
iGluRs	Ionotropic glutamate receptors
IL-1	Interleukin-1
IL-18	Interleukin-18
IL1β	interleukin 1β
IL-6	Interleukin-6
InsP3R	inositol 1,4,5-trisphosphate receptors
KIF5a	kinesin family member 5a
LTP	long-term potentiation
MAPK	mitogen-activated protein kinase
mGluRs	metabotropic glutamate receptors
Miro	mitochondrial Rho GTPases
mTOR	Mammalian target of rapamycin
NE	Norepinephrine
NFTs	neurofibrillary tangles
NF-κB	nuclear factor kappa light chain enhancer of activated B cells
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate receptor
NOX	NADPH oxidase
NOX2	NADPH oxidase-2
nPKC	calcium-indipendent PKC
Nrf2	nuclear factor erythroid 2–related factor 2
NSC	neural stem cells
OS	Oxidative Stress
PANX1	Pannexin 1
PI3-Akt	phosphoinositide-3-kinase - protein kinase B
PICALM	Phosphatidylinositol Binding Clathrin Assembly Protein
PINK1	PTEN-induced kinase 1
PKC	Protein kinase C
PRAS40	AKT1 Substrate 1
PSEN1	presenilin-1
PSEN2	presenilin-2
PTK2B	Protein Tyrosine Kinase 2 Beta
RAGE	Advanced Glycation Endproducts Receptors
RIN3	Ras And Rab Interactor 3
RNS	Radical nitrogen species

ROS	Radical oxygen species
RyR	ryanodine receptor
SAD	sporadic AD
SOCE	store-operated Ca2+ entry
SORL1	Sortilin Related Receptor 1
TGF β	Transforming Growth Factor-β
TNF-α	Tumor necrosis factor α
Trak1	trafficking kinesin protein 1
VEGF	Vascular-Endothelial Growth Factor
VEGFR2	Vascular endothelial growth factor receptor 2
VGCC	voltage-gated Ca2+ channels
Wnt	Wingless-related integration site
α7nAChRs	α7 nicotinic acetylcholine receptor
αSyn	α-synuclein

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