Chapter 3

Comprehensive Overview of Alzheimer's Disease Neurodegeneration, from Amyloid-β to Neuroinflammatory Modulation

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Additional information is available at the end of the chapter

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Abstract

Alzheimer's disease (AD) constitutes a major health threat to elder people. Despite the great advances achieved regarding our knowledge of the disease, we are far to successfully treat this pathology. Molecular alterations, immune/inflammatory response, and cell death are some of the processes involved during the pathology. Moreover, AD affects the whole brain. In this regard, we must not only consider the health status of neurons, of course, but also pay attention to the status of the glial cells and additional surrounding structures, such as the blood-brain barrier (BBB). Several groups have demonstrated how the molecular alterations occurring during AD alter neurons, glial, and endothelial cells. This situation has become so relevant that different groups are currently working to unveil the blank spaces in our understanding about the co-involvement of these elements in AD. Based in our experience, we believe that this kind of approach will lead to the design and development of more comprehensive therapeutical interventions. The present chapter summarizes the relevant aspects of state of the art regarding AD, from its molecular genesis to the recent advances in neuroinflammatory modulation, including nuclear receptors (NR), such as peroxisome proliferator-activated receptors (PPARs), and the Wnt pathway involved in the AD neurodegeneration.

Keywords: Alzheimer's disease, neurodegeneration, amyloid-β, neuroinflammation, Toll-like receptors, glial activation, TREM2

1. Introduction

Scientific progress has given enormous benefits to human population. In this regard, the continuous advances in biomedicine have constituted one of the more relevant achievements

of the last centuries. Increased rate of newborn survival, control of devastating infectious pathologies, chirurgical management of systemic pathologies, and increased life expectancy of the world population are some of the milestones reached because of science development.

Although positive, the increased longevity of world population has led to two critical events, which have huge implications in human health. On one side, our biological system must work for a longer period of time. Considering that no machine can work indefinitely without failure, the alteration/impairment of our cellular and molecular mechanisms should be considered as part of the price to live longer and as an open door for the development of several diseases. On the other side, we must consider that a longer life span also implies an increased exposition time to different kinds of xenobiotics. Environmental pollutant levels have increased along with the population growth, and although huge efforts have been committed to reduce the usage of the more toxic chemicals worldwide, just a rapid revision of the lists published by the International Agency for Research on Cancer (http://www.iarc.fr) allows us to understand and to dimension the threats usually faced during our life span. Accordingly, the increased incidence and prevalence of several chronic-degenerative pathologies, including cancer and neurodegenerative disorders, should not be a surprise. Indeed, age and the exposition to environmental pollutants are considered as the main risk factors for the establishment and progression of these pathologies. Thus, to properly face this specific type of alterations, a complex equation should be solved, including deep knowledge of the cellular and molecular mechanisms behind each disorder and the environmental elements able to induce, perpetuate, and/or accelerate the pathophysiological processes.

In the present chapter, we will focus our efforts to summarize the most relevant aspects regarding Alzheimer's disease (AD) and the key elements of its pathophysiological process. Moreover, we will include relevant information and discussion about some aspects of neuroinflammatory modulation.

2. Alzheimer's disease

Described more than a century ago, Alzheimer's disease (AD) constitutes nowadays an extremely complex public health threat. With up to 10% of people over 65 years old affected by this pathology and up to 50% of people over 85, AD is the most common form of dementia worldwide. Moreover, the cost associated to AD has been estimated in USD 818 billion. Additionally, the social implications should be considered when the total impact of the disease is addressed. Indeed, according to Alzheimer's Research International, in most cases, the relatives of an AD patient are those who take care of the patient health, causing a huge impact in the familial economy as well as social stress [1].

To date, two presentation forms have been reported for AD: the familial or early-onset AD (EOAD) and the late-onset AD (LOAD). As suggested by its name, the main characteristic of EOAD is its presentation before the 65 years old, with cases reported from the 30s to 60s and with a high genetic background at least in three genes (amyloid precursor protein, *APP*; presenilin 1, *PSEN1*; and presenilin 2, *PSEN2*). Although no consensus has been agreed, several

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researchers have defined that EOAD might reach the 5% of total AD cases worldwide. On the other hand, the LOAD occurs after the 65 years old, and age and life style are considered as the main factors leading to AD insurgence. Importantly, in both presentation forms, the apolipoprotein E (*ApoE*) ε4 gene allele has been identified as a relevant risk factor (**Figure 1**) [2].

Clinically, AD progresses from the compromise of the short-term memory to long-term memory loss and cognitive impairment. The selective neuronal death within memory and learning brain areas is at the basis of these clinical alterations. Indeed, frontal cortex, limbic area, and hippocampus atrophies along with extracellular accumulation of amyloid-β (Aβ) plaques and intra-neuronal neurofibrillary tangles (NFTs), constituted by hyperphosphorylated *tau* protein, are pathological hallmarks of the disease [3]. Additionally, increased oxidative stress status, mitochondrial dysfunction, impaired energy metabolism, and altered autophagy process have also been demonstrated during the disease. Importantly, the spread of these alterations across the different brain areas ultimately leads to neuronal network failure, affecting the synapses critically, and to the loss of function of these areas [3, 4].

On the other hand, it is important to realize that AD affects the whole brain. In this regard, we must consider the health status of neurons, of course, but also pay attention to the status of

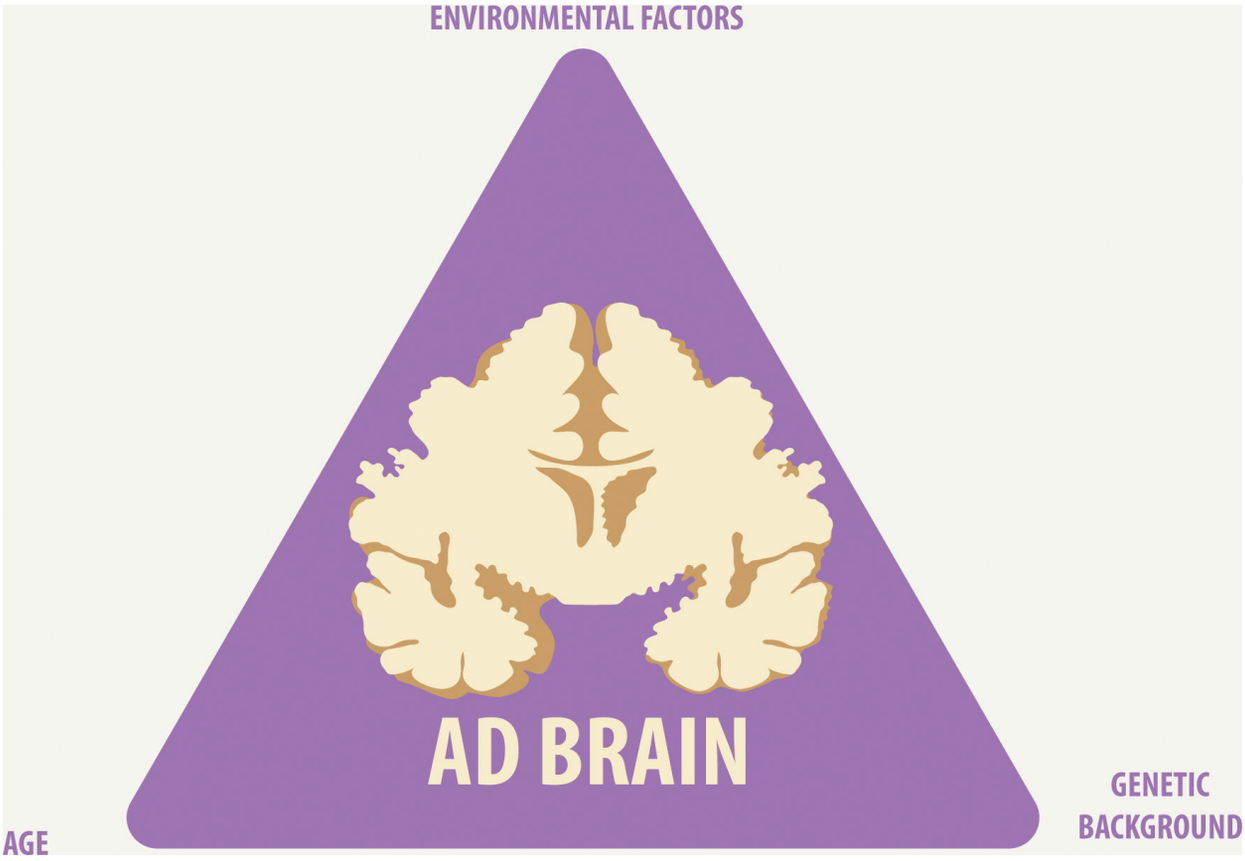

Figure 1. Etiological factors of AD. A simplified view. Alzheimer's disease is a highly complex disease. Although several risk factors have been identified, the etiology of this disorder remains elusive. Environmental factors, such as exposure to common pollutants; aging, which not only accounts for a decrease in the natural defenses of the organism but also increases the exposure time to the environmental contaminants; and the genetic susceptibility, such as the ApoE ε4 allele or presenilin mutations, create the perfect conditions to facilitate the establishment and progression of AD.

the glial cells and additional surrounding structures, such as the blood-brain barrier (BBB) [5]. Several research groups have demonstrated that the molecular alterations occurring during AD not only alter neurons but also microglia, astrocytes, pericytes, and endothelial cells, as well; and more importantly, each of these cells will respond to the molecular insults triggering a subsequent series of molecular events able to affect itself as well as the neighboring cells and tissues [5–7]. Whether these subsequent events are just the consequence or part of the cause/progression of AD is still matter of research.

2.1. Alzheimer's disease amyloid hypothesis

Since its description in 1906 by Dr. Alois Alzheimer, several hypotheses have been proposed to explain the pathobiology of the disease. Based on initial neurochemical studies of AD brains, an altered metabolism of acetylcholine (ACh) in the basal forebrain of AD patients was reported. This finding leads to the formulation of the "cholinergic hypothesis" of AD in which the ACh deficiency at the cortical level is considered responsible, at least in part, of the cognitive and behavioral impairment observed during disease progression. Moreover, ACh deficiency has been linked to NFT formation, and an increased activity of the ACh-esterase (AChE) has been found surrounding the Aβ plaques [8]. On the other hand, "*tau* hypothesis" was proposed in attention to the presence of NFTs across the brain and because this alteration seems to correlate better with the cognitive impairment observed as disease progress. In the same way, *tau* hyperphosphorylation and aggregation can also explain several of the molecular and physiological events related to the pathology, including synaptic failure, mitochondrial dysfunction, Aβ aggregation, and neuronal death, among others. Other relevant features of AD, the senile plaques, have also lead to its own hypothesis. Indeed, already in 1985, it was suggested that AD was an amyloidosis phenomenon, similar to other pathological processes, in which the Aβ accumulation starts a series of event leading to neuronal death and cognitive impairment. The observations of such events have led to the "amyloid hypothesis" of AD and, to date, constitute the main axis behind AD-oriented basic and applied research [4, 9].

As mentioned previously, the amyloid hypothesis states that AD will result from the increased accumulation of Aβ within the brain. Accordingly, several authors have suggested that the accumulation will result from an altered equilibrium between the production and elimination rate of Aβ from the brain [10–12]. Aβ constitutes a small posttranscriptional processing product of the ubiquitous amyloid precursor protein (APP), a transmembrane protein, coded in chromosome 21, which has been linked to nerve differentiation and cell adhesion and signaling. Physiologically, APP can undergo two clearly defined processing pathways. The non-amyloidogenic processing is carried out by the alpha (α) and gamma (γ) secretases, which lead to the release of the soluble APPα (sAPPα) and the p3 fragment. On the other hand, when this process is carried out by the beta (β) and γ secretases, the amyloidogenic pathway is established and leads to the release of the sAPPβ and the neurotoxic Aβ peptide (**Figure 2**) [9, 12].

Ranging from 37 to 49 amino acids, Aβ constitutes the critical molecular event at the basis of the AD establishment and progression [9]. Although Aβ can interact with other molecular elements and organelles, a relevant feature of this peptide is its ability to self-aggregate, being able to constitute monomers, oligomers, fibrils, or bigger aggregates, such as plaques [3, 8].

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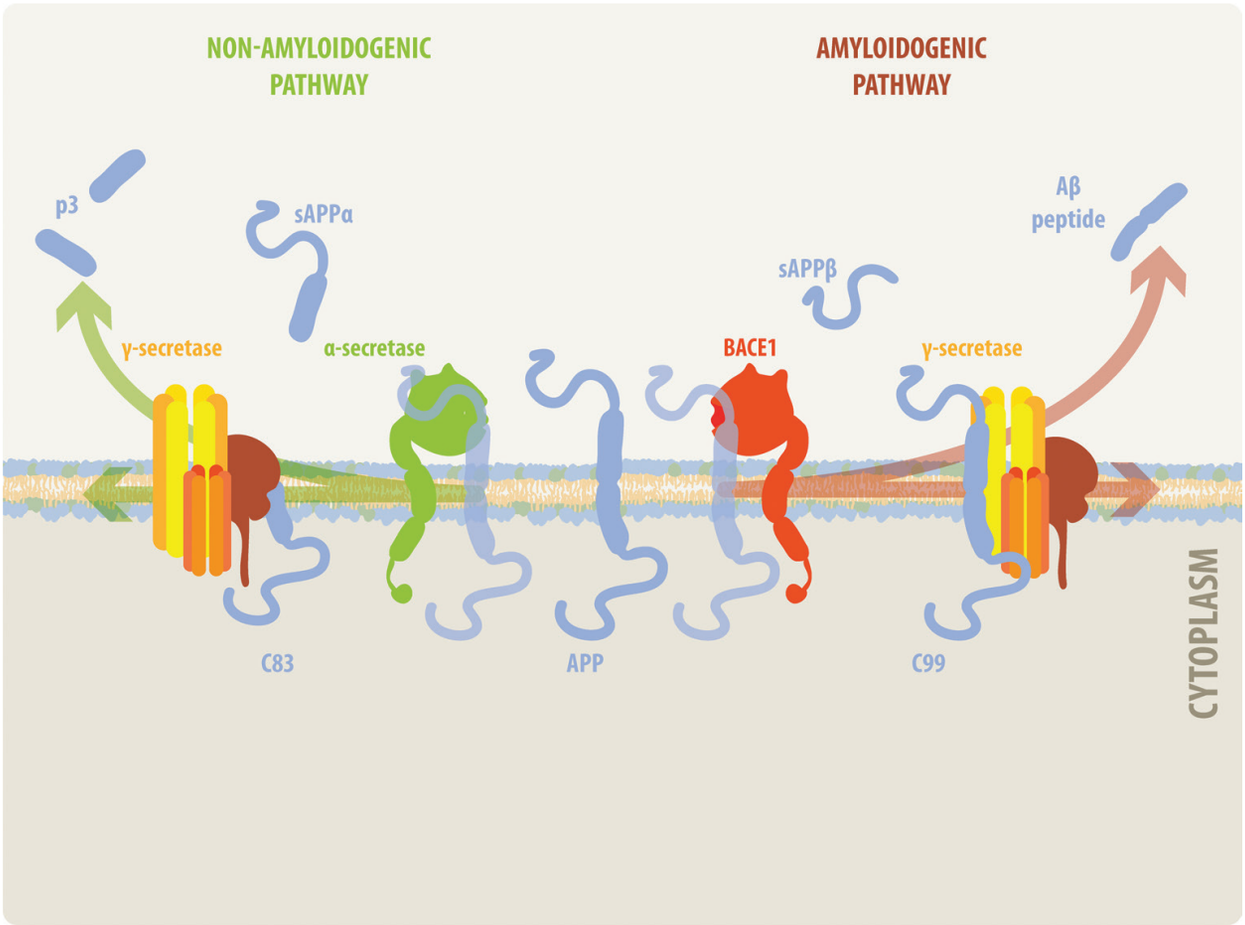

Figure 2. Apolipoprotein processing pathways. APP can be processed according two known paths. The non-amyloidogenic pathway will require α- and γ-secretase activity and will lead to the release of the sAPPα and the p3 peptide, both small peptides with a poorly understood function. On the other hand, when β- and γ-secretases work sequentially, the formation of the sAPPβ and the Aβ peptide, the main neurotoxic agent described in AD, will be favored. Importantly, external factors can increase the expression levels/activity of β-secretase, suggesting the potential upregulation of the amyloidogenic processing of the APP. sAPPα/β, soluble APP fragment α/β; p3, 3-KDa peptide; BACE, β-site APP cleaving enzyme.

Importantly, each of these forms has its own implications in terms of reactivity and toxicity. During several years, the plaques were considered the most harmful element of the AD pathophysiology. Indeed, the dystrophic neurites, reactive astrocytes and microglia, and increased activity of AChE commonly found around the plaques were considered as clear indicators that these formations were responsible for the progression of the pathology [8]. However, currently, it has been accepted that the oligomeric Aβ is the most neurotoxic form, which needs to be controlled to avoid AD progression. Evidently, any circumstance able to favors the amyloidogenic processing of the APP, would increase the risk of developing AD due to increased levels of Aβ [9, 11]. Down syndrome (chromosome 21 trisomy leads to an additional copy of the APP gene), upregulation of γ-secretase activity (presenilins 1 and 2), upregulation of the β-site APP cleaving enzyme (BACE, β-secretase) activity, downregulation of non-amyloidogenic APP processing enzyme (A disintegrin and metalloprotease, ADAM, 9–10 and 17) activity, and increased APP enzymatic processing hotspots within the plasma membrane

(lipid raft) are some of the conditions able to increase the Aβ production rate within the brain, causing its subsequent accumulation [11–16].

On the other hand, the Aβ removal occurs mainly through the blood stream and, in a lesser extent, through the cerebrospinal fluid (CSF). Apolipoprotein E (ApoE) constitutes the Aβ chaperone, necessary to mobilize the peptide from the interstitial fluid (ISF) to the blood-brain barrier (BBB) transport system and/or to the choroid plexus to its final elimination from the brain [9, 10]. Although several members of the ATP-binding cassette family of transporters, such as ABCB1, ABCC2, and ABCG4, can be linked to the Aβ removal, the low-density lipoprotein receptor-related protein/ApoE receptor (LRP/APOER) is the main responsible of the Aβ clearance through the BBB. Contrarily, the receptor for advanced glycation end products (RAGE), a transmembrane receptor of the immunoglobulin superfamily located at the luminal side of the cerebral microvasculature, allows the influx of Aβ from the blood stream to the brain parenchyma [5, 6, 9, 17].

When the balance between production and clearance is altered, the Aβ levels start to increase within the brain interstitial fluid (ISF) where finally it will start to aggregate and exert its neurotoxic effects in the surrounding cells. Although Aβ-derived damage is considered as an extracellular process, it has been also suggested that the intracellular accumulation of Aβ might play a relevant role at the early stages of the disease. In this regard, APP has been found in different cell compartments including the Golgi apparatus, endoplasmic reticulum, endosomes, lysosomes, and mitochondria. Moreover, cell uptake has been also evidenced through the α7 nicotinic acetylcholine receptor, suggesting that in the presence of increased extracellular levels of Aβ, the peptide can enter the cell and starts to accumulate within the intracellular space, probably causing the first cellular alterations, including *tau* hyperphosphorylation and neurite atrophy [9].

Although no hypothesis can be discarded, amyloid hypothesis is considered as the most relevant one because the molecular cascade and cellular effects observed during AD can be tracked backward to the Aβ peptide. Moreover, in vitro, in vivo, and human studies have evidenced that Aβ-directed interventions can prevent or slow the progression of the disease. In the same way, more recently, studies focused to improve the clearance of Aβ from the brain have shown promising results as potential AD drugs [4, 10, 18].

As pointed previously, AD pathophysiology is a very complex disease, with a multifactorial etiology which, to date, is still matter of intense research. Moreover, even when we have been able to establish that the clinical signs correlate with the impairment of the neuronal network and neuronal loss, the broad range of molecular alterations still seem like little islands in the sea. In this regard, Aβ has been proposed as a central element in the pathology and as the starting point for all the molecular and cellular alterations found at the different stages of the disease. However, several questions, like how disease spreads across the brain, are still open. During the recent years, the neuroinflammatory response has been identified as a relevant feature of the AD brain, and it has been suggested that disease progression might be due, at least in part, to a chronic neuroinflammatory state of the brain [19–21]. Again, Aβ can be located at the center of this process leading to additional alterations which can further promote an exacerbated inflammatory response within the brain.

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3. Aβ: the core of the immune/neuroinflammatory response in Alzheimer's disease

Inflammation is a fundamental physiological process to solve tissue damage. In general, pathogens and/or toxic elements disturb the cellular environment, triggering a whole range of responses including complement cascade activation and cytokine release from the injured cell and from the immune cells located at the site of the insult. The final goal of such response is to eliminate the initial cause of distress and cell debris and to repair of the damaged tissue. In this regard, pro-inflammatory and anti-inflammatory cytokines, such as tumor necrosis factor 1 (TNF-1α), interleukins (IL-1, IL-8, IL-10), interferon (INF-γ), and transforming growth factor 1 (TGF-1), along with complement proteins, develop a coordinated response to constitute a solid first line of defense against many unspecific damaging agents [19, 21]. Although this mechanism is common to the whole organism, the central nervous system (CNS) and the brain possess some particularities, which need to be addressed.

The CNS is a highly specialized structure, and neurons are recognized to require specific microenvironmental conditions to carry out its functions and to ensure that neuronal network is properly functioning. Although the CNS is partially isolated, preventing both external and internal elements to alter the brain homeostasis, eventually, some external insults, such as pathogens or environmental pollutants, and/or endogenous conditions, such as autoimmune diseases, sterile pathological processes, and aging, among others, will reach the brain parenchyma and induce neuronal damage that will require an efficient immune response to control and to prevent the spreading of the damage. It is important to consider that the brain parenchyma constitutes an anti-inflammatory environment with high expression of relevant anti-inflammatory mediators, such as transforming growth factor b (TGFb) and interleukin (IL)-10 [22, 23]. Although common systemic immune cells and molecules, such as cluster of differentiation 11b- and 11c (CD11b, CD11c)-positive cells, can be found in the CNS during the immune/inflammatory response, these factors mainly localize close to BBB-damaged areas, suggesting that its migration might be due to an increased BBB permeability [24]. Interestingly, an important feature of the anti-inflammatory molecules localized in the brain is to prevent peripheral immune cell proliferation. This condition establishes microglia and astrocytes as the specialized cells responsible to carry out the immune surveillance and to act as the first line of response against harmful events within the brain. Even when these characteristics might prompt us to consider the brain, and the CNS, as an immune-incompetent organ, it has been proposed that the mentioned conditions are necessary to prevent strong and uncontrolled immune/inflammatory responses, which can cause further neuronal damage [24]. However, under pathologic conditions, such as AD, in which a harmful molecule, such as Aβ, accumulates and aggregates within the neurons and ISF, a chronic inflammatory condition can still be triggered leading to the involvement of the different cells and structures within the brain, including neurons and brain microvasculature, among others (**Figure 3**). Interestingly, during

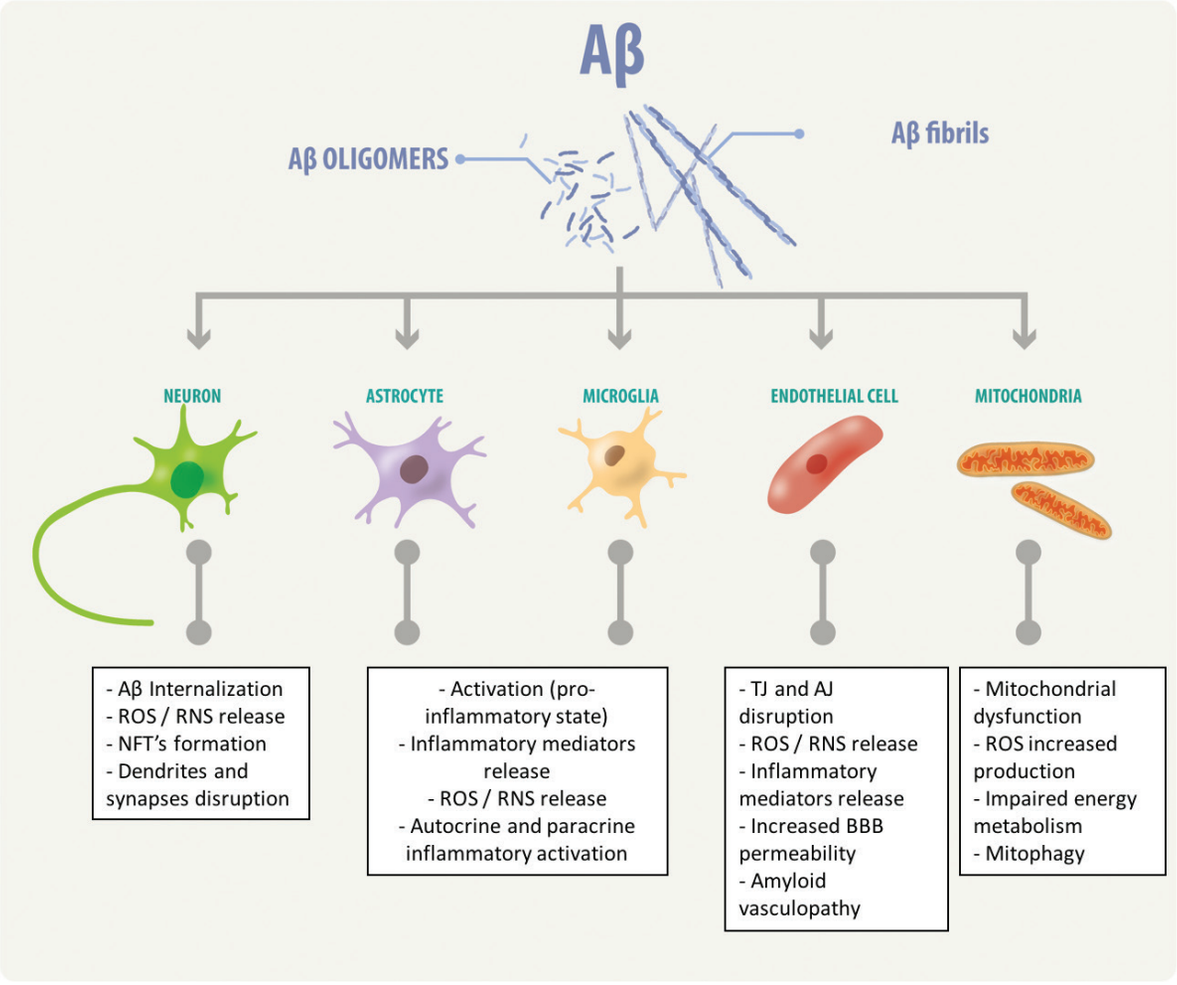

Figure 3. Amyloid-β-mediated effects on cells and organelles. Whether as oligomers or fibrils, Aβ is able to induce several effects on cells and on subcellular compartments. Aβ-derived damage and/or response will trigger a cascade of events, which ultimately will affect a wide range of CNS elements. Neuroinflammation is a common outcome of Aβ exposure. Upon Aβ challenge, neurons will release pro-inflammatory mediators. Moreover, neurons can internalize the Aβ affecting the neuronal trafficking and leading to cytoskeleton alterations, such as NFT formation. On the other hand, astrocytes and microglia will be activated inducing the production and release of pro-inflammatory mediators, which in turn can further activate surrounding glial cells and neurons. In the same way, Aβ will also deposit around cerebral microvasculature, leading not only to the release of additional inflammatory molecules but also to the disruption of the BBB sealing, allowing the extravasation of blood components to the brain parenchyma, altering the CNS microenvironment. Similarly, it has been demonstrated that Aβ can enter the mitochondria where it will cause mitochondrial dysfunction with an increased production of ROS, which will increase the oxidative stress within the surrounding cells, further inducing an inflammatory response. These events will occur simultaneously and together will sustain a persistent inflammatory response which will perpetuate and enhance the initial Aβ damage.

recent years, the Aβ-driven neuroinflammation has become significantly relevant and currently is considered as a critical target to control AD [5, 25]. Moreover, it has been demonstrated that permanent exposure to Aβ due to an increased production or deficient clearance from the brain will lead to a chronic inflammatory state, which results in a harmful environment for the neurons, causing additional damage and ultimately further neuronal death. Importantly, the inflammatory mechanisms triggered by Aβ are driven mostly through the Toll-like receptor (TLR) family [20].

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3.1. Toll-like receptors (TLRs) and Aβ

The TLR family constitutes a relevant group of the pattern recognition receptors (PRRs), a subtype of the damage-associated molecular patterns (DAMPs), which are endogenous indicatives of cell damage. As PRRs, TLRs are necessary not only to unleash the initial immune response but also to connect this first unspecific defense with the secondary adaptive immunity [20]. In this regard, TLRs have been demonstrated to be present in several cell components and in immunocompetent cells of the brain, including astrocytes, microglia, neurons, and oligodendrocytes, suggesting that each of these cells can sense and react to harmful molecular patterns [26, 27]. Moreover, it has been demonstrated that microglia and neurons express all TLR subtypes, whereas astrocytes express a more limited repertoire, including TLR2, TLR3, TLR4, TLR9, and TLR11 [28, 29]. Several members of the TLR family have been described, depending on the species, and these can be divided into two main groups: those expressed on the plasma membrane, such as TLRs 1, 2, 4, 5, and 6, and those expressed on endosomes, such as TLR 3, 7, 8, and 9. In general terms, TLRs signal through the myeloid differentiation factor 88 (MyD88) pathway. Accordingly, MyD88 recruitment leads to the activation of interleukin 1 receptor-associated kinase (IRAK) family of proteins, which in turn results in the activation of tumor necrosis factor receptor-associated factor 6 (TRAF6), causing the recruitment of transforming growth factor-b-activated kinase-1 (TAK1). TAK1 along with TAK1-binding proteins (TABs) activates the IKK complex, resulting in the phosphorylation of IkB factor, which induces the release of nuclear factor-kB (NF-kB) and enables its translocation to the nucleus and subsequent expression of inflammatory-related genes. However, some TLRs, such as TLRs 3 and 4, can signal via an additional pathway mediated by TIR-containing adaptor inducing interferon-β (IFN-β) (TRIF). Although this pathway results in the release of NF-kB, it also causes, via the IKKe/TANK-binding kinase 1 (TBK1), the phosphorylation of interferon regulatory factors 3 and 7 (IRF3–IRF7), inducing IFN-β expression. At the end of these TLR-related molecular cascades, we observe the production and release of several molecular mediators, such as cytokines, chemokines, complement proteins, and enzymes, including IL-1, IL-6, IL-10, IL-11, IL-12, tumor necrosis factor (TNF), TGF, IFN, CCL2, CCL5, CXCL8, and CXCL10, among others [26–29]. Among the several effects exerted by these molecules, these can further activate the TLRs, reactivating the inflammatory cascade.

Relevantly, Aβ has been demonstrated to interact with several members of the TLR subfamily of receptors, including TLR2 and TLR4, inducing an immune response with the subsequent release of pro-inflammatory molecules, including several members of the interleukin family, such as IL-1β, IL-6, IL-12, TNFα, cyclooxygenase 2 (COX2), and inducible nitric oxide synthase (iNOS) [30]. As previously mentioned, microglia, astrocytes, neurons, and oligodendrocytes express several members of TLRs, making them able to respond both to the Aβ insult and to the inflammatory mediators released in response to Aβ [20]. In this regard, it has been demonstrated that IL-6 levels are significantly elevated in AD and that its increased expression can be achieved by both direct production after primary Aβ exposure of the microglia, astrocytes, and/or neurons and as a secondary response to pro-inflammatory mediators such as IL-1β [31].

3.2. Neurons

As mentioned, Aβ induces the secretion of pro-inflammatory molecules and/or exerts mechanical damage to the neurons, altering its delicate metabolism and leading to neuronal dead. Moreover, it will induce the release of additional inflammatory mediators, such as reactive oxygen and nitrogen species (ROS and RNS), which are able to interact with several biomolecules, including membrane lipids, nucleic acids, and proteins. As a result, synapses, dendritic projections, myelin sheath, and cell structure will be altered, compromising neuronal functionality [32–34]. Additionally, it is well known that increased BBB permeability is one of the primary alterations in AD, leading to the loss of brain isolation allowing systemic components to enter the brain parenchyma, altering the neuronal microenvironment [5]. As this condition is sustained in time, such variation will further damage neurons triggering and spreading the inflammatory response [9].

On the other hand, several authors have proposed that Aβ can also drive the hyperphosphorylation of *tau* protein, altering neuronal cytoskeleton and impairing the neuronal network. Indeed, it has been demonstrated that Aβ can be incorporated to the neurons, altering the synapses also through a *tau*-mediated mechanism. In this regard, it has been demonstrated that *tau* modifications lead to frontotemporal dementia without Aβ deposition, but Aβ alterations induce the full range of AD pathology, including NFTs. Importantly, this *tau*-mediated cytoskeleton alterations might induce neuronal apoptosis causing the release of DAMPs which will be sensed by the TLRs located in the surrounding cells, including glial cells and neurons, and triggering an inflammatory response [3, 4, 6, 8].

3.3. Astrocytes

Astrocytes are fundamental to sustain brain homeostasis. These cells carry out several critical functions for neuronal function including, but not limited to, offering metabolic support to neurons and synapses and regulation of the neurotransmitter concentration. Astrocytes also play a relevant role in the inflammatory response [35]. Indeed, reactive astrocytes are a common feature of neuroinflammation and are usually considered as an indicator of the inflammatory state of the brain. In this regard, it has been demonstrated that the activation of TLR and NF-κB within astrocytes induces the production of pro-inflammatory molecules including IL-1; IL-6; TNF; chemokines, such as CCL2 and CC3CL1; and proteins of the major histocompatibility complex (MHC). Additionally, astrocytes have been syndicated as the responsible for the excitotoxicity damage because of glutamate release during harmful stimuli [21, 36]. Importantly, in response to the inflammatory signals, astrocytes can proliferate, migrate, and produce further inflammatory mediators, some of which are able to act in a paracrine manner activating the surrounding cells, including microglia, neurons, resting astrocytes, and endothelial cells [37].

On the other hand, a particularity of astrocytes is that these cells produce the ApoE, the main Aβ chaperone which allows the removal of the peptide from the brain. Altered astrocytes or genetic conditions, such as ApoE ε4 allele expression, will cause an impaired ApoE activity leading to a reduced rate of Aβ clearance, facilitating its accumulation and triggering the

inflammatory response observed upon Aβ exposure [10]. In the same way, it must be noticed that astrocytes are in close contact with the BBB through the astrocytic end-feet, being able to sense the intracerebral microenvironment but also to be the first to response to increased BBB permeability [5–7].

3.4. Microglia

Microglia reach the brain before the BBB closure and are defined as the main effectors of the immune response acting as the macrophages of the brain. Microglia remain in a "resting" state until diverse stimuli trigger the activation of these cells inducing the inflammatory response. It has been demonstrated that the resting state is maintained because of the interaction between the microglial chemokine (C-X-C motif) receptor 1 (CXCR1) and CD200L, with the neuronal CX3CL1 and CD200, respectively [38, 39]. As expected, activation of the microglia will be induced when these inhibitory interactions are loss or inflammatory signals are sensed by the resting microglia. In this regard, activated microglia is being able to phagocyte the surrounding tissue, proliferate, and migrate where needed. Moreover, activated microglia will release additional pro-inflammatory molecules, such as TNF-α or IL-1β, as well as ROS and RNS [37].

Among the several receptors that allow the microglia to sense the surrounding environment, the Toll-like receptors (TLR 1-9) and its co-receptor CD14 are the most important for microglial activation. Regarding Aβ, certainly, TLR2 and TLR4 are fundamental and drive main of the microglial reactions to Aβ, including phagocytosis [20]. Relevantly, during the last few years, an important genetic component has emerged regarding microglial response. Complement receptor 1 (CR1), cluster of differentiation 33 (CD33), and triggering receptor expressed on myeloid cells 2 (TREM2) have been related to microglial-mediated Aβ phagocytosis. Although it has been evidenced that these three genes help to sustain the phagocytic phenotype of the microglial cells, TREM2 has emerged as a potential biomarker due to its increased levels found in the CSF in AD [40–42]. Moreover, it has been reported that TREM2 mutations, such as arginine 47 to histidine (R47H), are critical for Aβ plaque formation because of an impaired function and expression of the receptor within the microglia. Indeed, such mutations seem to facilitate TREM2 ADAM/γ-secretase processing, as evidenced by the increased levels of the soluble TREM2 fragment within the plasma and CSF in AD [43]. The significance of such findings is just emerging, and intense research are focused to elucidate the roles of TREM2 and its soluble fragment in the pathophysiology of neurodegenerative disorders.

3.5. Blood-brain barrier

Although the concept of the BBB was proposed in the 1900s, only recently it has attracted high attention due to its relevance in the neurodegenerative disorders. Importantly, along with the blood-CSF barrier and the arachnoid epithelium, the BBB is a fundamental part of the brain isolation system. Indeed, several researchers have demonstrated, using hydrophilic compounds, that polar solutes were unable to cross the BBB because of occluding tight junctions (TJ) established between adjacent endothelial brain cells [5]. Moreover, brain endothelial cells evidenced the expression of a highly complex proteome, necessary to efficiently conduct the traffic of different molecules form the brain to the blood stream and vice versa. These

characteristics clearly demonstrate that the BBB is an active player in maintaining the cerebral microenvironment. Furthermore, it is widely known that Aβ transport across the BBB is the main way to remove the Aβ from the brain. Due to its electrochemical characteristics, Aβ requires specialized transport to cross the BBB [6, 7]. The LRP1 and LRP2 and some members of the ABC family of transporters are related to brain Aβ clearance. Evidently, any pathological condition able to alter the brain microvasculature and, particularly, the endothelial cells will have a tremendous impact in the brain homeostasis and can affect the Aβ levels within the brain. In this regard, it has been demonstrated that Aβ accumulates around the blood vessels, leading to neurovascular dysfunction and cerebral amyloid angiopathy. Indeed, several changes take place in the cerebral blood vessels of AD patients, including loss of vascular density, decreased luminal diameter of vessels and capillaries, and thickness of vessel walls. More importantly, several of these alterations occur at the early stages of the disease. In attention to this observation, several authors have suggested that the BBB alteration might not be only a consequence of the neurodegenerative process but could be the basis of the pathological changes observed during the course of the disease [5–7, 9].

3.6. Mitochondria

Although an organelle, mitochondria should be addressed because one of the critical features of the Aβ-mediated damage precisely relates with mitochondrial dysfunction [3, 5]. Moreover, mitochondria constitute the power supply within cells, and each of the functions that have been reported in this section requires important amounts of energy to be carried out. In this regard, mitochondrial activity will depend on cellular status, and pathological conditions able to modify internal cell environment will absolutely have an impact on mitochondrial fate. Increased oxidative status or proapoptotic stimuli will trigger different cellular mechanisms conducted to control cell death and the destruction of cell organelles, such as the mitochondria. In this regard, it has been demonstrated that beyond inflammatory cascade, Aβ is able to induce several proapoptotic signaling including endoplasmic reticulum stress, with the intracellular release of Ca^{2+} which will overload the mitochondria, and ROS-mediated apoptosis through the apoptosis signal-regulated kinase (ASK1) and favors the apoptosis through the B-cell lymphoma 2 (BCL2)-beclin1 (BECN1) complex, among others [44, 45]. Moreover, it has been found that Aβ can also enter the mitochondria, leading directly to mitochondrial dysfunction and to altered energy metabolism within cells. Along with the reduction of available ATP, altered mitochondria will also increase the production of ROS contributing to increase the brain oxidative status and resulting in the production of additional pro-inflammatory mediators, such as IL-6 [44–47]. In this regard, once released to the extracellular compartment, ROS can further trigger the inflammatory pathways in the neighboring cells inducing the activation of the NF-kB-dependent pro-inflammatory cascade [20].

4. New insights of neuroinflammatory modulation in Alzheimer's disease

As evidenced previously, the inflammatory response has demonstrated to be highly relevant in several neurodegenerative disorders, including AD, Parkinson's disease, Huntington's

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disease, multiple sclerosis, and amyotrophic lateral sclerosis. In these disorders, inflammation verifies since the early stages of the neurodegenerative process, and it is believed that it can also accelerate the spread of the disease across different brain areas. Moreover, several experimental therapeutic approaches have evidenced that controlling neuroinflammation might improve the disease outcome. Accordingly, during the last decades, huge efforts have been committed to understand neuroinflammation and how to control such process. Although several molecular pathways can be tracked down to explain the neuroinflammatory cascade, some of these pathways, such as nuclear receptors (NR) and the Wnt signaling, seem to develop a critical role in this kind of processes because it usually plays a pivotal role in the cellular physiology.

4.1. Nuclear receptors

Nuclear receptors (NR) constitute a highly conserved superfamily of proteins [48]. These receptors act sensing the intra- and extracellular microenvironments and exert several functions including embryogenesis, reproduction, metabolism, inflammation, immunity, and lipid signaling. An important feature of its structure is that several domains can be recognized which upon activation, mainly through ligand binding, will induce conformational changes allowing the exposure of functional domains to the consensus nucleotide sequence present in the target genes, inducing their expression [49].

Peroxisome proliferator-activated receptors (PPARs) are classified as type II NR, which are characterized by the formation of heterodimers with the retinoid X receptor (RXR). PPARs possess a four-region structure including an amino terminal region, AF-1, which functions as a constitutive ligand-independent transactivation domain: the DNA-binding domain (DBD), constituted by two zinc fingers which recognize and bind the specific DNA nucleotide sequences termed peroxisome proliferator response element (PPRE), which consists of two AGGTCA sequences separated by a single nucleotide. Importantly, this domain contains the necessary elements to allow dimerization with the RXR. Next, the Hinge region is found and is believed to allow to connect the DBD to the ligand-binding domain (LBD). The LBD is a well-conserved domain among species, which is characterized by the presence of the ligand-binding pocket, a 12–13 anti-parallel α-helix structure. Within this region, there is also a ligand-dependent transactivation (AF-2) domain, which is intimately involved with both the generation of the ligand-binding pocket and interaction with transcription coactivators. Three PPAR isoforms have been described. Generally, PPARα is expressed in the liver, kidney, and skeletal muscle; PPARβ/δ is widely expressed, including the CNS; and PPARγ is highly expressed in fat tissue [49]. Importantly, several researchers have demonstrated the expression of the three PPAR isoforms within the brain, including the hippocampus, the critical brain area related to memory (**Figure 4**) [50].

Activation of the PPAR/RXR heterodimer will lead not only to the DNA binding but also to the exposure of the AF-2 domain, which will interact with the LXXLL motifs present in several PPAR coactivators, including the receptor family p160/steroid coactivator (SRC), p300/CREB-binding protein (CBP) complex, the switching/sucrose non-fermenting (SWI/SNF) chromatin remodeling complex, the PPAR interacting complex (PRIC) 285, and PRIC320/chromodomain helicase DNA-binding protein 9 (CHD9) [51]. Each of these coactivators, which have

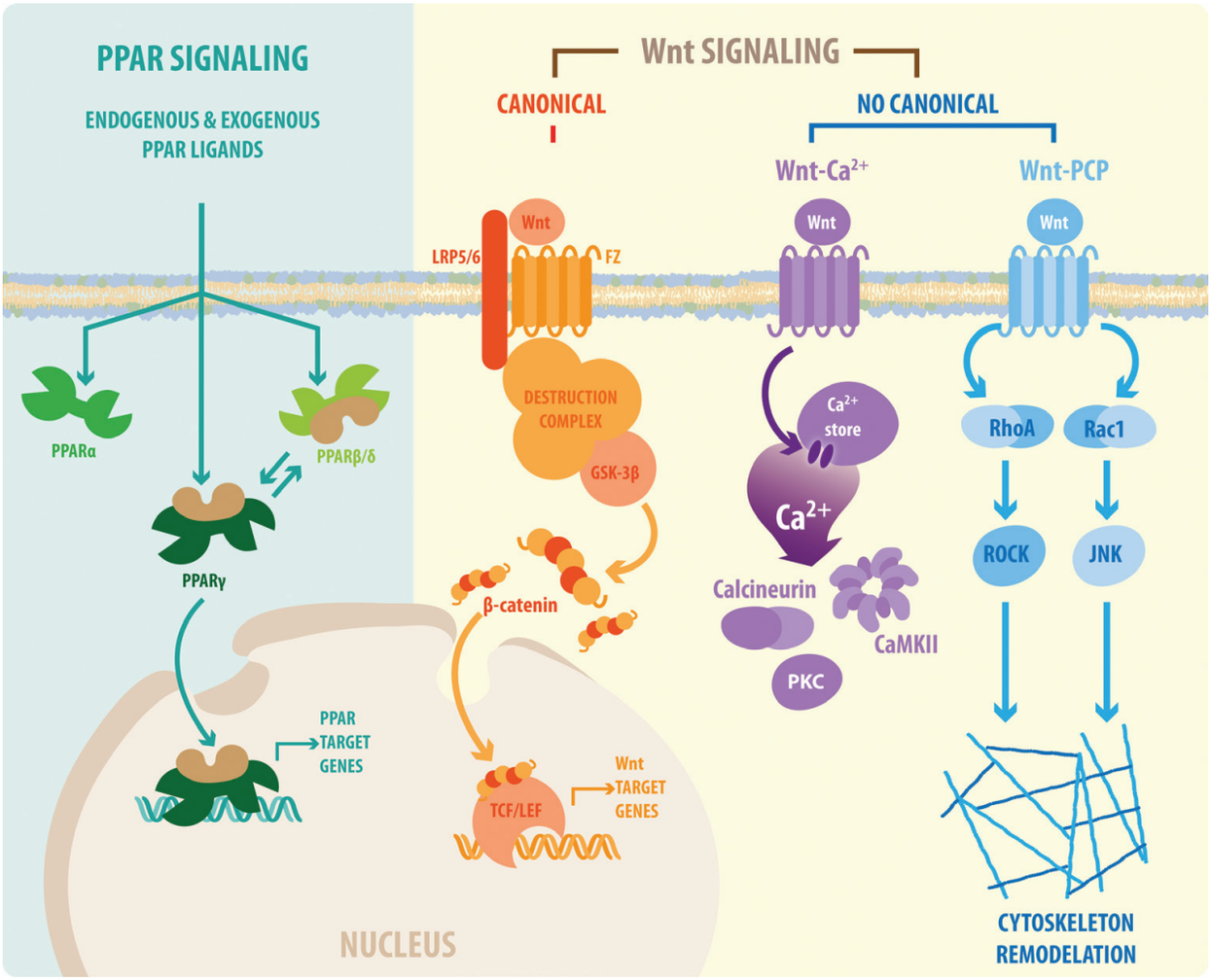

Figure 4. PPARs and Wnt pathways. The figure represents the common molecular cascades associated to PPARs and Wnt signaling. Type II nuclear receptors, such as PPARs, form heterodimers with the RXR. The PPAR/RXR dimer binds to the DNA through the consensus sequence (PPRE), inducing the expression of target genes. PPAR, peroxisome proliferator-activated receptor; PPRE, peroxisome proliferator response element. On the other hand, the Wnt signaling pathway can be divided into canonical Wnt signaling and noncanonical Wnt pathways. During activation, canonical Wnt ligands interact with the Fz-LRP5/Fz-LRP6 complex receptor, this situation leads to the disassembly of the β-catenin destruction complex, which prevents GSK3β-mediated β-catenin phosphorylation. Thus, β-catenin can translocate to the nucleus where it binds to the TCF/Lef, initiating the transcription of Wnt-related genes. The noncanonical Wnt pathway, known as Wnt/Ca^{2+}, can be triggered by noncanonical Wnt ligands. In this case, Fz will induce the release of calcium from intracellular stores, leading to the activation of calcineurin, CamKII, and PKC. In the same way, the noncanonical Wnt/PCP pathway also requires noncanonical Wnt ligands, which will interact with the Fz receptor and will activate Dvl. However, at this point, Dvl induces the activation of RhoA and Rac, which ultimately will lead to cytoskeletal rearrangement. Fz, Frizzled receptor; LRP, low-density lipoprotein receptor-related protein; GSK3β, glycogen synthase kinase 3β; TCF/Lef, T-cell factor/lymphoid enhancer factor; PCP, planar cell polarity; RhoA, Ras homolog gene family member A; ROCK, rho-associated protein kinase; Rac1, Ras-related C3 botulinum toxin substrate 1; JNK, c-Jun N-terminal kinase; PKC, protein kinase C; and CamKII, calcium/calmodulin kinase II.

enzymatic activity, increases the transcriptional activity of the PPARs mainly through the chromatin remodeling and/or stabilization of the PPAR-DNA binding. Additionally, PPARγ-coactivator 1(PGC-1α), a nonenzymatic PPAR coactivator, needs to be mentioned because it has demonstrated to be critically involved in the mitochondrial function, ther

mogenesis, andenergy homeostasis. PGC-1α also requires the AF-2/LXXLL association to increase PPAR transcription. Moreover, PGC-1α-PPAR binding induces a conformational change in PGC-1α that promotes its binding to SRC-1 and CBP/p300, further enhancing the transcriptional activity. It has been proposed that in the brain, PGC-1α plays an important role in mitochondrial oxidative metabolism and in the maintenance of intracellular calcium levels [52, 53].

As pointed in previous sections, increased levels of Aβ will induce microglial and astrocyte activation and neuronal alterations and can compromise additional cells and structures, such as the BBB. As the result of such increased levels of Aβ, production of several cytokines (TNF-α, IL-1β, S100β) and chemokines (MIP-1α, MIP-1β) as well as oxidative stress-associated molecules will be enhanced. Relevantly, PPARs have demonstrated very interesting properties regarding the modulation of the inflammatory response. In this regard, the most studied isoforms are the PPARα and γ. Inhibition of activator protein 1 (AP-1) and NF-κB signaling is one of the well-known effects of PPARα and γ activation [54]. However, signal transducer and activator of transcription (STAT-1), nuclear factor of activated T cells (NFAT), early growth response protein 1 (Egr-1), and Jun and GATA-3 expression are also inhibited by PPARγ [54]. Moreover, PPARα activation also leads to reduced expression of T-box transcription factor (T-bet) and to the impairment of its binding to the DNA, limiting the expression of the pro-inflammatory cytokine IFN-γ. On the other hand, PPARα induces the expression of GATA-binding protein 3 (GATA3), a master regulator of the anti-inflammatory molecule IL-4 [55]. Because of the PPARα and γ activation, the expression of several pro-inflammatory cytokines, including IL-1, IL-4, IL-6, IL-8, IL-12, and TNF-α; vasoactive mediators, including cyclooxygenase 2 (COX-2), iNOS, and endothelin-1; expression of adhesion molecules, such as ICAM-1; chemokines, such as MCP-1, MCP-3, and INF-γ-inducible protein 10 (IP-10); and metalloproteases, such as MMP-9, are often reduced [17, 38, 55, 56]. Regarding the PPARβ/PPARδ, it is also believed that NF-κB blockade might be part of its mechanism of action, but its role against neuroinflammation is known to be related to the regulation of pro-inflammatory molecules, including C-C motif chemokine ligand 2 (CCL2), IL-6, and IL-1β [57].

An additional relevant feature of the PPARs is its ability to eventually induce an improvement in the Aβ clearance ratio from the brain ISF. It has been evidenced that increased levels of ApoE, the Aβ chaperone, can improve Aβ removal rate lowering its levels and preventing its aggregation [10]. Interestingly, ApoE is a target gene of the liver X receptor (LXR), another type II NR, which in turn is a target gene of the PPARs. Although indirectly, this genetic cross relation can explain the beneficial effects observed after PPAR agonist administration in in vivo models of AD [5, 9].

4.2. Wnt signaling pathway

The Wnt signaling constitutes a relevant molecular system related to several physiological processes, including cell proliferation and differentiation. Wnt proteins are highly conserved among different species, and beyond its physiological roles, several studies have demonstrated the involvement of this family of proteins in pathological processes of the CNS, including neurodegenerative disorders, such as AD [58].

Classically, Wnt signaling can be divided in the canonical and noncanonical Wnt pathways. In the first one, also known as the β-catenin-dependent pathway, Wnt proteins bind to the Frizzled receptor/low-density lipoprotein receptor-related protein 5/Frizzled receptor/low-density lipoprotein receptor-related protein 6 (Fz-LRP5/Fz-LRP6), inducing the activation of the disheveled protein and the interaction between LRP5 and LRP6 with Axin. This interaction causes the disassembly of the β-catenin destruction complex constituted by the adenoma polyposis coli (APC), Axin, GSK3b, and casein kinase 1 (CK1), preventing the β-catenin phosphorylation and allowing its translocation to the cell nucleus where it will bind to the T-cell factor/lymphoid enhancer factor (TCF/Lef) transcription factor to induce the expression of Wnt target genes. Without the positive input of the Wnt ligands, the destruction complex remains active inducing the β-catenin phosphorylation and the subsequent proteasomal degradation. On the other hand, the noncanonical Wnt pathway can also be divided into two additional cascades: the Wnt/planar cell polarity (Wnt/PCP) pathway, which requires the binding of Wnt ligands and signals through disheveled-Rho and Rac GTPases, inducing c-Jun N-terminal kinase (JNK) activity and leading to actin cytoskeleton modeling, and the Wnt/Ca^{2+} pathway in which the binding of Wnt ligands to the Fz receptor induces the release of Ca^{2+} from intracellular compartments, including the ER, causing the activation of several calcium-related proteins, such as protein kinase C (PKC) and calcium-/calmodulin-dependent protein kinase (Ca^{2+}/CamKII) (**Figure 4**) [20, 58].

The Wnt signaling has emerged as a very promiscuous pathway. It has been possible to identify the crosstalk between both canonical and noncanonical signals which exert a modulatory effect over its counterpart. Moreover, Wnt pathways can also interact with additional molecular pathways, including the NF-kB, fork head box O (FOXO), Notch, hypoxia-inducible factor 1a (HIF1a), and JNK [52]. Indeed, several elements of the Wnt cascade seem to constitute molecular master switches that can be accessed through diverse mechanisms. This condition is of most relevance regarding the inflammatory response. Indeed, Wnt signaling has been directly associated with the control of the inflammatory process, mainly because of its ability to modulate the NF-kB pathway. However, the complex interaction established between this pathway and the master coordinators of the inflammatory response within cells has been constantly obviated. Moreover, it is well noticed that the canonical and noncanonical pathways exert, usually, opposed actions [20, 59]. While the canonical Wnt prevents the inflammatory cascade by blocking the NF-kB pathway, interacting with RelA, the noncanonical pathway has been reported to promote the inflammatory response, actin, through the PI3K, Rac1, and MAPK, and to the subsequent release of pro-inflammatory molecules. However, it must be considered that some noncanonical Wnt ligands, such as the Wnt5a, can exert an anti-inflammatory effect and vice versa [20].

We have recently suggested that in attention to the Wnt pathway-mediated NF-kB modulation, a crosstalk between the Wnt and TLR pathways seems to be evident [20]. Moreover, different authors have demonstrated that TLR activation downregulates the canonical Wnt signaling pathway. Indeed, TLR4 activation can block the Fz-LRP5/Fz-LRP6 complex inhibiting the canonical Wnt signaling [60]. Contrarily, the activation of the Wnt/Ca^{2+} induces the expression of the suppressor of cytokine signaling 1 (SOCS-1) and of protein inhibitors of activated STAT 1 (PIAS-1), causing a reduced expression of some signal transducers of the TLR cascade, such as IRAK members and MyD88. In the same way, the MyD88-mediated TLR

activity results in the activation of the nemo-like kinase (NLK), which directly interacts with the nuclear β-catenin-TCF/Lef complex. On the other hand, it has recently been demonstrated that MyD88-independent TLR signaling activates the IKKe/TBK1, which can directly phosphorylate Akt, leading to GSK3β inhibition, the key β-catenin degradation-driven protein. Moreover, the blockade of the GSK3β activity prevents the binding of NF-kB with the cAMP response element-binding protein (CREB)-binding protein (CBP), suggesting that GSK3β activity modulates the TLR-dependent cytokine production [61–64].

Interestingly, lithium, a well-known canonical Wnt signaling agonist because of GSK3β inhibition, allows to further address the role of Wnt signaling in neuroinflammation. In this regard, it has been demonstrated that lithium not only reduces the expression of pro-inflammatory mediators, such as IL-6, but it also reduces TLR4 expression in astrocytes [65]. Whether these effects are mediated directly by Wnt signaling or as a part of a secondary mechanism, GSK3β seems to play a pivotal role not only in the Wnt singling itself but also as the master switch in the context of the inflammatory response.

5. Final considerations

During the recent years, the relevance of the inflammatory process in the neurodegenerative disorders, such as AD, has evolved from a consequence of such pathological events to an early sign of brain distress. Moreover, the severity and chronicity of the inflammatory response within the brain parenchyma are believed to favor the progression and spreading of these diseases across the brain.

Understanding the inflammatory cascade, triggered after Aβ exposure, and the critical nodes which allow control the process is a fundamental goal to develop new and efficient therapeutical alternatives to fight AD. In this regard, our knowledge regarding Aβ-related inflammation has increased dramatically in the last years; however, relevant questions about the molecular mechanisms involved in such response are still open, with new players appearing each day. Nuclear receptors and Wnt signaling are two of the main cellular pathways able to modulate several cellular processes. Moreover, independently each of them has proven to be involved in the Aβ-induced inflammatory response; however, little is known about its interactions as part of the inflammatory molecular network. On the other hand, one of the more recent cases of new players identified to be relevant in neuroinflammation is constituted by the TREM2 protein, which favors Aβ microglial phagocytosis. Already known, this protein and its processing have recently emerged as novel and interesting biomarker and as a target to unveil some of the questions about the neuroinflammatory process observed during AD.

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