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Provisional chapter

Molecular Basis of Neurodegeneration: Lessons from Alzheimer's and Parkinson's Diseases

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Abstract

Alzheimer's disease (AD) and Parkinson's disease (PD) constitute the main causes of dementia worldwide and the major health threats to elderly people. Moreover, with the ageing of the global population, neurodegenerative disorders, such as AD and PD, constitute a major public health issue. Regrettably, significant advances regarding the molecular aspects of these diseases have not yet been translated into real improvements in AD/PD therapeutics. In this regard, both AD and PD are highly complex and involve critical molecular events governing the establishment and progression of each disease. Moreover, molecular alterations trigger pathophysiological cascades involving the immune/inflammatory response, oxidative stress, and mitochondrial dysfunction, among others, ultimately leading to neuronal death. Similarly, these alterations also affect glial cells and brain vasculature, which contribute directly to the progression of these disorders. Accordingly, the present paper aims to summarise the main molecular elements related to AD and PD as well as the pathophysiological implications of such alterations to improve our understanding of the cellular and molecular responses observed during neurodegeneration. We believe that providing a more comprehensive view of the pathophysiological cascade, including neurons and glial cells, might prompt researchers to widen neurodegenerative disorder research and therapeutic approaches.

Keywords: ageing, Alzheimer's, Parkinson's, amyloid-β, α-synuclein, neuroinflammation, oxidative stress, mitochondrial dysfunction

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1. Brief introduction to ageing

Undoubtedly, the increased life expectancy of the global population constitutes a major achievement of the modern world. However, it has also opened a gate for the development of age-related conditions that are far from completely understood. In this regard, age-related diseases, particularly neurodegenerative disorders, currently constitute a public health focal point. Accordingly, in recent years, much attention has been focused on understanding both the physiology of ageing and the critical events driving pathological ageing with the subsequent development of different age-related disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD) [1].

In this regard, ageing constitutes a natural, highly complex process that involves the progressive decay of several biological systems. Moreover, genetic and epigenetic heterogeneity introduces variation in the ageing process from one individual to another [2, 3]. In addition, an increased lifespan implies longer exposure to environmental pollutants that able to interact and modify different biological molecules, including DNA, not only affecting the functionality but also favouring the insurgence of several chronic degenerative disorders (http://www.iarc.fr). Indeed, an altered DNA repair system, systemic and cellular redox imbalance related to mitochondrial dysfunction, sustained pro-inflammatory conditions and impaired immune system functionality are some of the several age-compromised homeostatic systems that can be at the root of pathological changes observed during ageing. Relevantly, and as occurs in other chronic degenerative processes, the breakdown of the homeostatic control and the verification of these alterations seem to depend not only on the impairment of one of the compromised systems but also on the concomitant failure of and crosstalk among others.

As an example, it can be noted that although a reduced methylation status has been recognised as a common condition of the aged genome, the promoter hypermethylation of some genes, with subsequent gene silencing, has also been described [2, 4–7]. The promoters of MutL homologue 1 (MLH1) and MutS homologue 2 (MSH2), both part of the DNA mismatch repair system (MMR), have been reported to be hypermethylated due to arsenic exposure, suggesting an epigenetic-induced DNA MMR impairment that will increase the susceptibility of aged subjects to DNA damage [8]. Whether additional environmental pollutants or inner cellular metabolism end-products can modify the epigenetic control of such relevant mechanisms is an open question [9]. It is important to highlight that both MLH1 and MSH2 are related to the control of the impact that oxidative damage causes on DNA, and both have been observed to decrease during ageing [10]. Concomitantly, and in accordance with Harman's free radical theory [11], the redox balance has been well characterised in aged subjects, indicating that along with the age-related increased production of reactive oxygen and nitrogen species (ROS/RNS), mainly due to mitochondrial failure, the capability of different tissues, including the brain, to buffer ROS/RNS is diminished, as indicated by an increased oxidative status in older subjects [12, 13]. Indeed, the activity of the main ROS/RNS scavengers, including superoxide dismutase (SOD), catalase (CAT), glutathione (GSH) and glutathione peroxidase (GPx), has been demonstrated to decay with ageing, favouring ROS/RNS-related damage, such as lipid peroxidation, protein denaturation and DNA mutations [14, 15]. Moreover, mitochondrial dysfunction, which also constitutes a key element in ageing,

is considered one of the major components of the neurodegenerative process observed in both AD and PD. Importantly, beyond the energy impairment, mitochondrial alterations contribute significantly to the increased production of ROS/RNS, increasing the oxidative pressure on the redox equilibrium (**Figure 1**).

On the other hand, it has been well established that chronic exposure to increased levels of pro-oxidant species leads to the concurrent activation of the immune system and triggering of the inflammatory cascade, both further sustained by the release of several pro-inflammatory mediators, such as several interleukins (IL-1, IL-6, IL-8) and interferon-γ (IFN-γ) [16–19]. Moreover, inflammation and the immune response both involve nuclear factor κb (NFκb), a common point that crosslinks both responses. While toll-like receptors (TLRs), which are activated by different subcellular molecular components (damage-associated molecular patterns, DAMPs), signal through NFκb to release several pro-inflammatory cytokines, leading to activation of the immune response, the very same NFκb constitutes an oxidative stress sensor, connecting the increased levels of ROS/RNS with activation of the inflammatory cascade [20, 21]. Additionally, it must be considered that immunocompetence is usually compromised in aged individuals, and several authors have shown that this decay is closely linked to the altered epigenetic control of several immune-related genes [22–24]. Altogether, this evidence suggests that the difference between "normal" and pathological ageing lies in the subtle equilibrium of different homeostatic

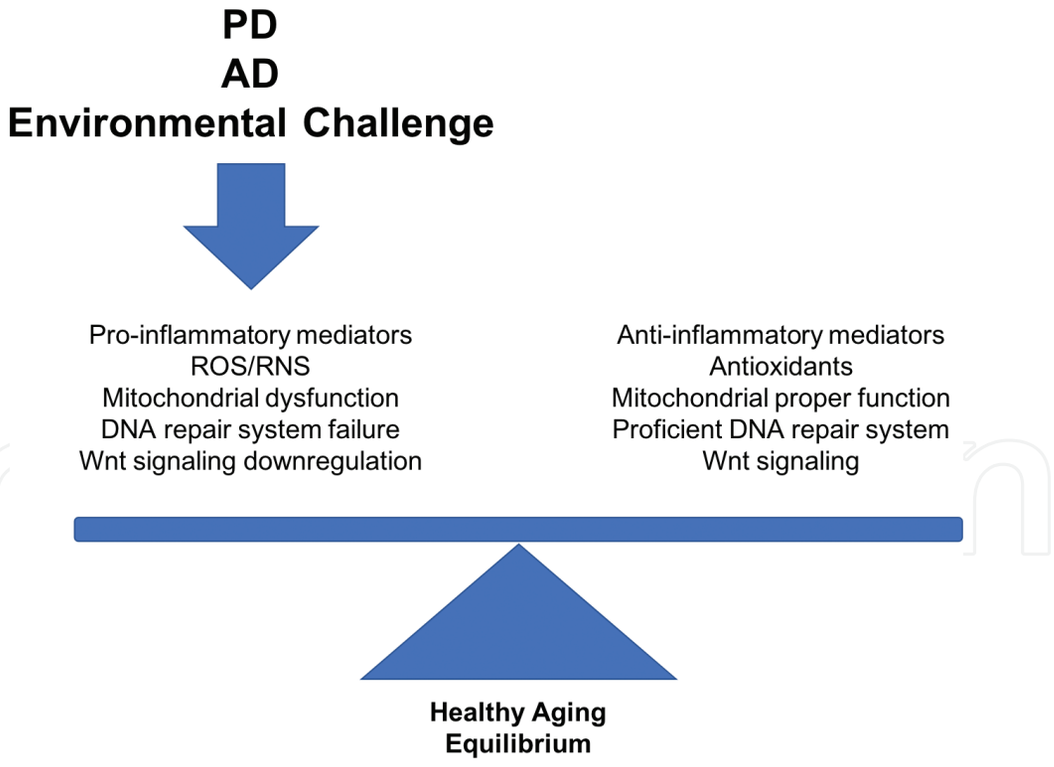


Figure 1. Homeostatic balance against pathological ageing, Alzheimer's disease (AD) and Parkinson's disease (PD). The delicate balance that sustains healthy ageing can be broken under several conditions. Environmental challenges, pathological processes, such as AD and PD, or ageing itself might introduce further pressure in different homeostatic systems, including the immune and redox systems. Moreover, the complex network of molecular alterations, organelle dysfunction and cellular signalling, among others, increases the difficulty of properly addressing the cloudy edge between healthy ageing, pathological ageing and age-related disorders.

systems that can become imbalanced with any additional external/internal stimulus, leading to failure of biological systems and the development of diverse pathological hallmarks.

In the following sections, we will summarise the most relevant aspects of AD and PD and the key elements of each pathophysiological process in the context of the delicate balance of an aged system.

2. Molecular event-driven neurodegeneration: lessons from AD and PD

AD and PD constitute the two most common age-related neurodegenerative disorders [1, 25], and their prevalence is expected to increase together with the ageing of the human population [1]. Although they are different entities, both disorders share some similarities regarding pathophysiological processes (**Figure 2**).

2.1. Alzheimer's disease

In general terms, AD compromises patient memory and cognitive performance. Initially manifesting as mood instability, the clinical scenario progresses from the compromise of short-term memory to the loss of long-term memory. As superior functions are lost, patients become absolutely dependent on a caregiver to complete even the most elementary tasks. Atrophy of the frontal cortex, limbic area and hippocampus due to neuronal death are the basis of these clinical alterations. Histopathologically, AD shows the extracellular accumulation of amyloid β (Aβ) plaques and the intraneuronal formation of neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein [26]. However, even when these molecular events are considered the hallmarks of AD, these alterations are accompanied by an increased oxidative stress status, mitochondrial dysfunction and a chronic inflammatory response, among others, which ultimately serve to explain the synaptic damage, neuronal loss and neuronal circuitry breakdown [26, 27].

Relevantly, although AD constitutes an age-related disorder, an early onset presentation linked to the genetic background should not be omitted. In this regard, while late-onset AD (LOAD) is associated with patients over 65 years old, familial or early-onset AD (EOAD) appears before this threshold, with cases reported as soon as 30 years old. Of course, in EOAD, there is a relevant genetic background in at least three genes (amyloid precursor protein, *APP*; presenilin 1, *PSEN1*; and presenilin 2, *PSEN2*). On the other hand, in the case of LOAD, age and lifestyle are considered to be the main causative factors. Importantly, the apolipoprotein E epsilon 4 (ApoEε4) allele has been identified as a relevant risk factor for both presentation forms [28].

Independent of the presentation form, and as noted previously, Aβ deposition and NFT formation constitute the key molecular features of AD. Moreover, considering that each of the additional pathological alterations often observed during progression of the pathological process can be derived from each of these two hallmarks, each of them has led to the development of individual hypotheses. Although the crosstalk between the amyloid and tau hypotheses is evident, it must be noted that the scientific community has not yet agreed on which one encompasses the whole spectrum of the disease, and the aetiological trigger of the pathological molecular cascade remains unknown.

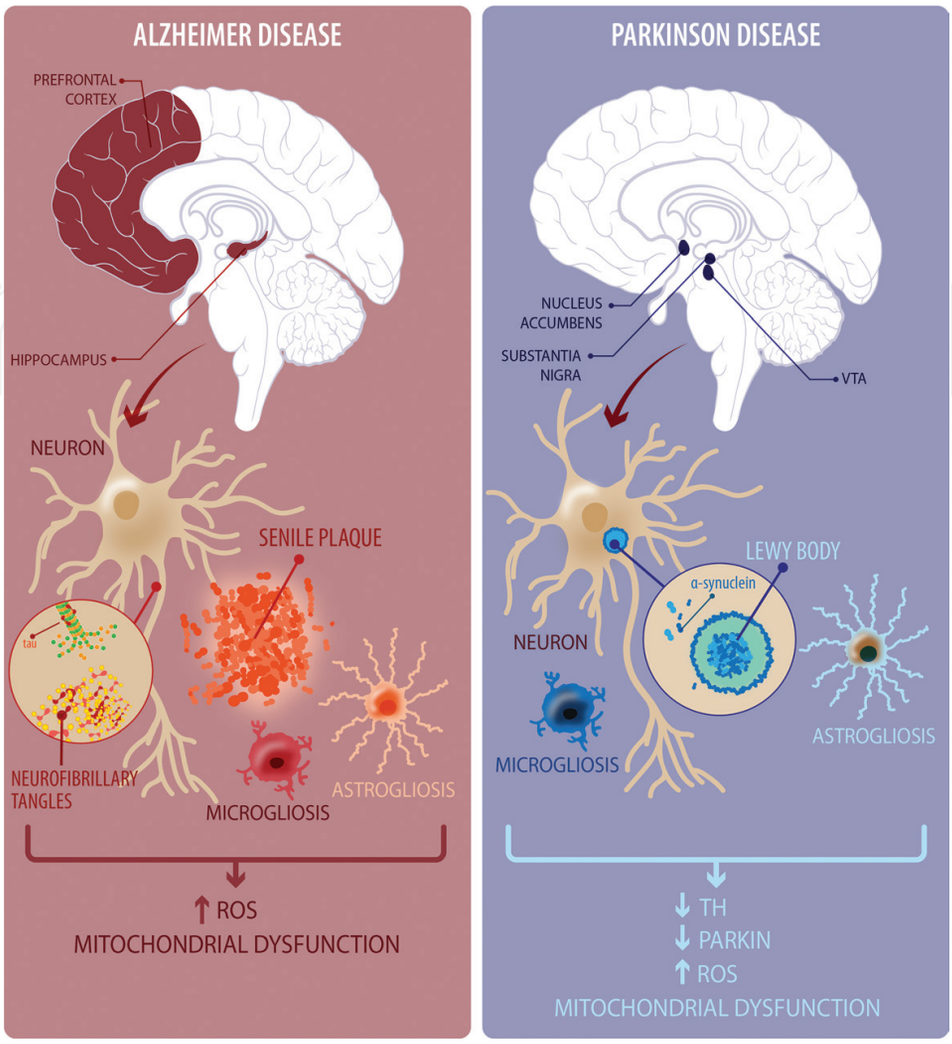


Figure 2. Alzheimer's disease (AD) and Parkinson's disease (PD). Pathological milieu overview. AD and PD are highly complex disorders. In both cases, in addition to the molecular hallmarks, cellular alterations are verified. Although several risk factors have been identified, the aetiology of both disorders is still unknown. AD is characterised by neuronal loss, mainly in the hippocampus. The pathognomonic feature of AD is the deposition of amyloid-β aggregates (senile plaques) and the formation of neurofibrillary tangles composed of hyperphosphorylated tau protein. These molecular alterations not only affect neurons but also induce microglial and astrocytic activation, leading to the release of several pro-inflammatory mediators. Additionally, cellular and molecular events will cause an increased production of reactive oxygen/nitrogen species, which will further damage the surrounding neurons and activate the surrounding glial cells, perpetuating the inflammatory response. In contrast, PD is characterised by the loss of dopaminergic circuitry beginning at the basal forebrain (substantia nigra pars compacta (SNpc), nucleus accumbens and ventral tegmental area (VTA)) and spreading to the striatum. The molecular hallmark of PD is the formation of Lewy bodies and neurites, which are composed of aggregated α-synuclein (SNCA), causing severe cellular stress affecting the cytoskeleton, neuronal trafficking and the synthesis of dopamine because of the direct inhibition of tyrosine hydroxylase (TH). SCNA can be exocytosed, causing it to be internalised by astrocytes, where it can further aggregate. Similarly, it will cause microglial activation. Neurons, astrocytes and microglia release pro-inflammatory mediators as well as ROS/RNS. A common feature of both disorders is mitochondrial dysfunction, which can be due to the pathological process or the result of the homeostatic imbalance verified during abnormal ageing.

Even with several additional hypotheses having been developed since the first description of AD by Dr. Alois Alzheimer, including the "cholinergic hypothesis" [29], from our limited expertise in the field, we approach AD considering the increased production and subsequent accumulation of Aβ within the brain as the starting point. Indeed, synaptic failure, mitochondrial dysfunction, tau hyperphosphorylation, glial activation and neuronal death, among

others, can be explained by the Aβ dynamics [27, 30]. According to this theory, AD results from the increased levels of Aβ, a 37- to 49-amino acid peptide derived from the proteolytic processing of APP, because of an unbalanced production/clearance rate [31–33]. In this regard, under the AD scenario, the non-amyloidogenic processing of APP, carried out by the alpha (α) and gamma (γ) secretases, which leads to the release of soluble APPα (sAPPα) and the p3 fragment, is overwhelmed by amyloidogenic processing, with beta (β) secretase (BACE1) as the main player, leading to an increased release of the neurotoxic Aβ peptide [30, 33]. On the other hand, under balanced physiological conditions, Aβ is cleared to the blood stream and cerebrospinal fluid (CSF), with the involvement of ApoE, the Aβ chaperone [30, 31], through several transporter proteins, including members of the ATP-binding cassette family of transporters, such as ABCB1, ABCC2 and ABCG4, and the low-density lipoprotein receptor-related protein/ApoE receptor (LRP/APOER), the main receptor responsible for Aβ clearance through the blood-brain barrier (BBB) [30, 34–36]. ApoE deficiency/incompetence (ApoEε4), altered Aβ-related transporter expression, choroid plexus and BBB damage will impair Aβ clearance, increasing brain Aβ levels. Additionally, the reduced activity of Aβ-degrading enzymes, such as disintegrin and metalloproteases (ADAM 9, 10 and 17A) and neprilysin, will further contribute to its accumulation within the brain [32, 33, 37–40]. At this point, the increased levels of Aβ will favour its self-aggregation, leading to the formation of different Aβ species, such as oligomers, fibrils and/or even larger aggregates, such as plaques [26, 29]. Moreover, the presence of APP together with its proteolytic machinery within the subcellular compartments, such as the Golgi and endoplasmic reticulum (ER), as well as the presence of Aβ peptide in the mitochondria, suggests that the intracellular APP dynamics can also be part of the pathological scenario along with the extracellular accumulation of Aβ peptide. Indeed, it has been demonstrated that in the presence of high levels of Aβ, the peptide can enter the cell through the presynapticα 7 nicotinic acetylcholine receptor and that this influx could be the basis for tau hyperphosphorylation, thereby causing neurite atrophy and synapse failure [30].

2.2. Parkinson's disease

PD is the second most common neurodegenerative disorder and can be classified as a synucleinopathy. It is characterised by failure of the dopaminergic circuitry because of the loss of dopaminergic neurons of the substantia nigra pars compacta (SNpc). Histopathologically, PD shows neuronal inclusions of aggregated α-synuclein (SNCA) protein in both the cell soma and neurites, forming Lewy bodies and neurites [25]. Although the effects of the loss of dopaminergic neurons help to explain the symptomatology, mainly associated with motor compromise, the mechanisms by which SNCA aggregates in relation to the whole molecular and clinical picture have remained elusive. Ranging from non-motor symptoms, including hyposmia and sleep disturbances, PD progresses to bradykinesia and rigidity and can be accompanied by impairments in memory, mainly prospective memory [25, 41, 42].

Similar to AD, genetic background also accounts for a small proportion of PD cases worldwide. β-Glucocerebrosidase (GBA), leucine-rich repeat kinase 2 (LRRK2), SNCA, parkin (PRKN), protein/nucleic acid deglycase (DJ1) and phosphatase and tensin homologue (PTEN)-induced putative kinase 1 (PINK1) have been recognised as the most relevant genes associated with PD presentation [25, 43]. On the other hand, sporadic PD has been related to age and lifestyle,

mainly regarding exposure to different types of chemicals, including agrochemicals and drugs [25, 44]. With the increase in life expectancy, the global PD prevalence is expected to double over the next decade.

As noted previously, independent of the presentation form, SNCA aggregates constitute the pathological hallmark of PD. In this regard, SNCA corresponds to a monomeric 140-amino acid protein localised at the presynaptic terminal, which is thought to be involved in the recycling of synaptic vesicle pools [45–47]. Although 50% of the protein can be found at the cytosolic level within the terminals, the remaining SNCA is associated with the membrane of both vesicles and early endosomes. Indeed, SNCA has been described as a chaperone protein of the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins [48]. However, the mechanisms related to the interaction of SNCA with SNARE or additional presynaptic proteins, such as Piccolo/Bassoon or Rab, and its function in regulating the dynamics of the synaptic terminal are still unknown [43, 49, 50]. Under pathological conditions, SNCA changes from a monomeric membrane-associated protein to an unbound monomer capable of forming β-sheet aggregates, which ultimately will form SNCA amyloid fibrils [50–52]. Moreover, SNCA can not only interfere with tyrosine hydroxylase, the dopamine synthesis enzyme, affecting both its expression and activity [53], but also interact with the dopamine transporter (DAT) [54]. At this point, and considering the altered synaptic vesicle dynamics, the dopaminergic synapse is severely compromised, constituting the basis of the PD synaptopathy. Additionally, similar to AD, this initial molecular event can be related to the additional features observed during the pathological process, including mitochondrial dysfunction, increased oxidative stress, and neuroinflammation.

3. Pathophysiological cascade in AD and PD

3.1. Inflammation and the CNS

Immunocompetence constitutes a fundamental feature for ensuring the preservation of any living organism. The rapid and coordinated elimination of potentially harmful elements is critical to maintain organism homeostasis and prevent irreversible damage to biological systems. In this regard, the innate and adaptive immune systems constitute the two subsystems that able to detect and induce a primary unspecific response to pathogens, coordinate a secondary response and develop an immune memory, the hallmark of adaptive immunity. As the first response element, the innate immune system depends on the effectiveness of several unspecific elements, including physical and chemical barriers, the complement system, the activity of surveillance cells, and inflammation. Through these complementary elements, a fundamental physiological process is triggered to constrain the insult and repair the damage. In general, whether because of a pathogen, toxic and/or damaged-cell end-products, the cellular microenvironment will change, leading to the activation of immunocompetent cells and causing the release of pro- and anti-inflammatory cytokines, such as tumour necrosis factor 1α (TNF-1α), interleukins (IL-1, IL-8, IL-10), interferon γ (INF-γ) and transforming growth factor 1 (TGF-1), to orchestrate a coordinated response against the primary insult, limiting its damage [55, 56]. Importantly, to appropriately answer signals of harm/damage, surveillance cells

need to express several types of receptors. Moreover, considering that harm/damage signals can be both exogenous, such as those from bacteria and viruses, and endogenous, such as those from DNA or ATP, these receptors should be able to interact with a wide range of these elements. Among the latter, TLRs constitute a key element of the innate immune response related to sterile inflammatory pathological processes, such as AD and PD. It is important to highlight that even when it was initially considered an immune-privileged system, because of its high specialisation and partial isolation from the rest of the organism, the central nervous system (CNS) is able to generate full-range immune responses. In this context, microglia and astrocytes are responsible for immune surveillance in the CNS, with microglia being the only immune-derived cells within the brain. Due to the critical role of the brain microenvironment, evidence suggests that the inflammatory response is tightly controlled to prevent the detrimental effects of an exacerbated process. Indeed, it has been determined that the brain parenchyma constitutes an anti-inflammatory environment with relevant levels of TGF and IL-10 [57, 58].

3.2. TLR-mediated neuroinflammatory response

TLRs are able to detect DAMPs, which are subcellular components, such as ATP, released into the extracellular media reflecting cell damage. Several members of the TLR family have been described and can be expressed at the plasma membrane, such as TLRs 1, 2, 4, 5, and 6, or in association with endosomes, such as TLRs 3, 7, 8, and 9. Importantly, TLRs are expressed by brain cells, including astrocytes, microglia, neurons and oligodendrocytes, with microglia and neurons expressing all TLR subtypes and astrocytes expressing a more limited repertoire, including TLR2, TLR3, TLR4, TLR9 and TLR11 [59, 60]. Briefly, the TLR-mediated modulation of the inflammatory response begins with the recruitment of myeloid differentiation factor 88 (MyD88), causing activation of the IL-1 receptor-associated kinase (IRAK) family of proteins. IRAK activates TNF receptor-associated factor 6 (TRAF6), causing the recruitment of TGF-β-activated kinase 1 (TAK1). TAK1, along with TAK1-binding proteins (TABs), will activate the IKK complex, causing phosphorylation of the IkB factor and the subsequent release of NF-kB to translocate into the nucleus, leading to the expression of NF-kB-related inflammatory genes. Importantly, TLRs 3 and 4 can also signal via a secondary TIR-containing adaptor inducing an IFN-β (TRIF)-mediated pathway. Additionally, in the latter case, NF-kB will be released, but IFN-β will be produced because of the phosphorylation of IFN regulatory factors 3 and 7 (IRF3–7) via IKKe/TANK-binding kinase 1 (TBK1). Independent of the cascade triggered through TLRs, the final outcome will be the production and release of cytokines, chemokines, complement proteins and enzymes, including several members of the IL family, such as IL-1, IL-6, IL-10, IL-11, and IL-12, as well as TNF, TGF, IFN, CCL2, CCL5, CXCL8 and CXCL10 [59–62]. An additional clue about the necessity of tightly controlling this process within a highly specialised organ, such as the brain, emerges from the property of these molecules to further activate TLRs, a situation that can lead to re-activation of the inflammatory cascade and a state of chronic inflammation.

In this regard, the inflammatory component of AD and PD has been demonstrated to be fundamental for both pathological processes. Moreover, it has been shown that both Aβ and SNCA can induce direct activation of the inflammatory response and that their sustained accumulation and aggregation lead to the genesis of a pro-inflammatory environment [21, 63,

64]. Indeed, during the recent year, the modulation and control of the inflammatory cascade have emerged as target elements of future therapeutic interventions aimed at improving AD and PD outcomes [34, 64, 65].

3.2.1. TLRs and Aβ peptide in AD

Evidence indicates that TLR2 and TLR4 are able to react with Aβ, leading to the release of several pro-inflammatory mediators, such as IL-1β, IL-6, IL-12, TNF-α, cyclooxygenase 2 (COX2) and inducible nitric oxide synthase (iNOS) [66]. As noted previously, such receptors are expressed by different cell types present in the brain, suggesting both the whole-brain commitment to the inflammatory response and the potential contribution of all these cells to the further release of pro-inflammatory mediators. In this regard, of the most relevance is the self-perpetuation of the inflammatory cycle induced by the continuous release of these molecules. Some of the pro-inflammatory cytokines, such as IL-6, which can be produced as part of the response to the initial insult (Aβ), can also be a consequence of the secondary effect induced by other cytokines, such as IL-1β [67]. Thus, if this response is not controlled, the environment can be perfectly suited to a sustained pro-inflammatory status that will overwhelm homeostatic mechanisms and damage the surrounding tissue.

Furthermore, Aβ can trigger additional molecular events within neurons. Beyond its pro-inflammatory effects, it has been demonstrated that Aβ can induce the hyperphosphorylation of tau protein, which will alter the neuronal cytoskeleton, ultimately leading to neuronal apoptosis with the release of further DAMPs [26, 27, 29, 35]. Evidently, this situation can also promote TLR activation, contributing to perpetuation of the inflammatory cycle. Similarly, astrocytes, which express a more limited repertoire of TLRs, are also fundamental for adequate Aβ metabolism. In the case of AD, astrocytes are responsible for the release of ApoE, the Aβ chaperone protein necessary for its removal from the brain. In this context, defective astrocytes, such as inflammatory-challenged astrocytes, or ApoE-related genetic conditions, such as the ApoEε4 allele, can lead to impaired ApoE activity, causing an increase in the Aβ level [31]. Again, these astrocyte-related conditions can compromise the brain's ability to resolve the inflammatory process and further contribute to enhancing a detrimental inflammatory response. In contrast, microglia, as the only representative of the immune system within the brain parenchyma, are the main cells responsible for surveying and initiating the immune response against exogenous and endogenous insults, acting as the macrophages of the brain. Microglia develop a close interaction with neurons through microglial chemokine (C-X-C motif) receptor 1 (CXCR1) and CD200L, with neuronal CX3CL1 and CD200, respectively [68, 69]. In the absence of a challenging stimulus, microglia remain in a non-inflammatory or "resting" state. However, when inflammatory signals, such as the loss of neuronal contact or DAMPs, are detected, microglia undergo morphological and physiological changes leading to an inflammatory or "activated" state. Among the several receptors expressed by microglia, TLRs 1–9 and the co-receptor CD14 are the most important for its activation [21]. Although it has been demonstrated that Aβ directly activates TLR2 and TLR4, it has recently been shown that additional elements are involved in the activity of microglia in response to aggregated forms of Aβ. Complement receptor 1 (CR1), cluster of differentiation 33 (CD33) and triggering receptor expressed on myeloid cells 2 (TREM2) have proven to be necessary for the successful phagocytosis of Aβ [70–72]. Moreover, it has been suggested that TREM2 acts as a receptor

for Aβ, thereby modulating the microglial inflammatory response [73]. The relevance of the functions related to TREM2 activity has led us to consider its proteolytic products (soluble TREM2) as potential biomarkers for AD, mainly because sTREM2 levels have been reported to be elevated in the plasma and CSF of AD patients [73–75]. The precise impact of such findings is just emerging, and some discrepancies have already been identified regarding which should be the appropriate approach to a TREM2-related intervention [76, 77].

3.2.2. TLRs and SNCA in PD

Similar to Aβ, different research groups have shown that SNCA induces the inflammatory response through a TLR2- and TLR4-mediated mechanism, leading to TNF-α, IL-6 and CXCL1 expression via the MyD88-NF-kB pathway [78–80]. Interestingly, it has been demonstrated that while monomeric SNCA activates TLR2, the oligomeric forms tend to activate TLR4 [81]. Complimentarily, a relevant issue has emerged from recent research which has demonstrated that inflammation itself, through a caspase-mediated mechanism, can favour the aggregation of SNCA [51, 52]. This latter finding further support the idea of a self-sustained cycle which amplifies the initial damage exerted by the SNCA and contributes to the progression of the pathology. However, beyond the TLR-NF-kB axis and the production of pro-inflammatory mediators, additional aspects should be considered regarding SNCA hallmarks.

Within neurons, aggregated SNCA, whether in the soma or in neurites, will cause cell death with the subsequent release of cellular content, the components of which will release additional DAMPs capable of interacting with additional TLRs [82]. Moreover, it has been demonstrated that SNCA can be exocytosed actively from neurons, incorporated by the surrounding astrocytes, and then further aggregated, causing the formation of inclusion bodies within the new host cells [83]. Considering that the primary function of astrocytes is related to providing metabolic support to neurons and modulating the neurotransmitter metabolism within synapses, the SNCA pathology will not only involve the inflammatory response of astrocytes but will compromise its physiology, enhancing the neuronal network damage verified during PD pathophysiology [84–86]. On the other hand, although microglia will react to SNCA through TLRs, SNCA can also influence the activity of activated microglia against further pro-inflammatory signals, suggesting that SNCA can induce a priming effect on the microglia population, exerting a type of modulation on the strength of the inflammatory response [70, 87]. Thus, in the case of SNCA, this molecule can not only induce/perpetuate a pro-inflammatory status but also lead to an increased susceptibility to any inflammatory process.

3.3. Mitochondrial dysfunction

An additional common feature of both pathologies is the increased production of ROS/RNS. Indeed, an important end point of glial activation is that in response to the initial inflammatory trigger, Aβ in the case of AD and SNCA in PD, astrocytes and microglia will produce not only further inflammatory mediators, such as TNF-α and ILs, but also ROS/RNS [85]. The increased production of ROS and RNS will alter the surrounding microenvironment, and these species will be able to interact with the lipids of the plasma membrane, proteins and nucleic acids of the contiguous cells, ultimately affecting component of the neuronal circuitry, such

as synapses, axons and whole cell structures [88–90]. In this context, mitochondrial activity, which is fundamental to sustaining neuronal activity, is one of the major sources of the continuous production of superoxide anions. This highly reactive species, if not neutralised, will severely damage subcellular structures. Under regular conditions, superoxide anions are scavenged as soon as they are produced through hydrogen peroxide formation. However, under altered redox conditions, such as those during ageing, cellular mechanisms to manage both physiological and pathological ROS/RNS production are overwhelmed [12–15]. Thus, AD and PD cause additional pressure on the mitochondria in an already poorly balanced system.

In this regard, both Aβ and SNCA have been demonstrated to be able to alter mitochondria. While Aβ has been found within mitochondria, indicating a direct effect on mitochondrial functionality [91, 92], SNCA can impair mitochondrial function mainly via altered cell trafficking. Indeed, it has recently been suggested that the cytoskeletal alterations induced by SNCA will modulate the localization of dynamin-related protein 1 (Drp1), a key protein related to mitochondrial dynamics and whose malfunction will lead to mitochondrial dysfunction [93, 94]. Complimentarily, Aβ, and probably SNCA, can induce ER stress, leading to the intracellular release of Ca^{2+}, which can increase the mitochondrial challenge, leading to further ROS/RNS production and causing the subsequent activation of classical pro-apoptotic pathways, such as ROS-mediated apoptosis through apoptosis signal-regulated kinase (ASK1) and activation of the B cell lymphoma 2 (BCL2)-beclin 1 (BECN1) complex [91, 92]. It should not be forgotten that ROS/RNS can trigger the inflammatory response in surrounding cells, such as glial cells and neighbouring neurons, in a TLR- and DAMP-mediated manner. Moreover, it is possible that prior to the pathological process, these aged individuals have some degree of inflammation, oxidative stress and mitochondrial impairment, which might facilitate the establishment and/or progression of both diseases.

4. Wnt signalling in the context of AD and PD anti-inflammatory therapeutics

Currently, neurodegenerative disorders, especially AD and PD, are considered a major concern in public health because of the ageing of the global population. Although some progress has been made regarding pharmacological strategies, regrettably, no effective therapies are currently available to stop or reverse these pathologies. Among the alternative approaches to overcome such situations, the identification and further modulation of key cellular pathways involved in the pathophysiology of neurodegenerative disorders should not be underestimated. In this regard, even when it is well recognised that inflammation is one of the most relevant features of AD and PD, anti-inflammatory therapies have remained overlooked, although some epidemiological data have suggested a significant effect in terms of risk reduction with the use of some nonsteroidal anti-inflammatory drugs (NSAIDs) [95, 96]. Interestingly, the main effects related to the use of such a family of drugs have been observed prior to the onset of pathology; however, the efficacy of an anti-inflammatory therapy cannot be fully discarded. Indeed, the reasons behind the failure of some clinical trials exploring the beneficial effects of NSAIDs in AD and PD have not been properly addressed [97]. Moreover,

a quick search of scientific databases, such as PubMed, will return over 3000 and 1000 entries for AD and PD, respectively, when both "anti-inflammatory therapy" and "AD/PD" are used as search terms. This issue not only reinforces the fact that inflammation is a key element of both pathologies but also indicates that the inflammatory cascade is closely related to several signalling pathways that have been linked to the pathophysiology of these diseases. Regrettably, our understanding of these mechanisms is incomplete, limiting our capacity to properly address and exploit such relationships.

In this regard, over several decades, our laboratory has been working on Wnt signalling, a master cellular pathway involved in both physiological and pathological conditions. The activity of Wnt signalling varies with ageing depending on the tissue [98]. Specifically, in the brain, an overall downregulation of the Wnt pathway is observed, suggesting that some of the impairments associated with age might be mediated by this Wnt decay [98, 99]. Accordingly, this situation suggests that the rescuing of its activity might be a promising strategy to prevent and alleviate some of the pathological features of AD and PD.

4.1. Wnt signalling pathway

From the initial steps during embryogenesis to the less explored adult neurogenesis, the Wnt pathway constitutes the core molecular signalling pathway of cellular physiology. Its relevance is demonstrated by the evolutionary conservation of this system among different species, and its potentialities are cross-linked with the outcome of different neurodegenerative disorders, including AD and PD [100, 101].

The Wnt pathway is commonly divided into two canonical or β-catenin-dependent and non-canonical pathways, with the latter further divided into Wnt/Ca^{++} and planar cell polarity (JNK). Briefly, in the canonical pathway, the Wnt ligands bind to Frizzled receptor/low-density lipoprotein receptor-related protein 5/6 (Fz/LRP5/6) and the subsequent activation of Dishevelled. This situation leads to disassembly of the β-catenin destruction complex comprising adenoma polyposis coli (APC), Axin, GSK3β and casein kinase 1 (CK1), leaving β-catenin free to translocate to the nucleus and initiate transcription of the Wnt target genes together with the T-cell factor/lymphoid enhancer factor (TCF/Lef) transcription factor. In the absence of Wnt ligands, the destruction complex remains active, and GSK3b phosphorylates β-catenin, causing its proteasomal degradation. On the other hand, in Wnt/planar cell polarity, the binding of Wnt ligands will induce cytoskeletal rearrangements via JNK-mediated mechanisms; in the Wnt/Ca^{++} pathway, ligand binding induces the release of Ca^{2+} from 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) [21, 100].

Additionally, the different cascades described for Wnt signalling can interact with several cellular pathways, including the forkhead box O (FOXO), Notch and hypoxia-inducible factor 1 alpha (HIF1α) pathways [93]. Precisely, the wide range of molecular interactions established by Wnt signalling serves to explain how its altered activity can not only favour or directly induce different pathological conditions, including neurodegenerative disorders and cancer,

but also act as a relevant player in the ageing process. In this regard, we have recently demonstrated that the loss of Wnt signalling favours the appearance of several pathological markers linked to AD in a wild-type murine model [102]. Moreover, we found that Wnt signalling is involved in the neuronal energy metabolism and that its activation rescues energy imbalance because of improved glucose utilisation [103]. On the other hand, Wnt signalling also plays a relevant role in PD. It has been demonstrated that LRRK2 can interact with several members of the β-catenin destruction complex, including Dvl, Axin, GSK3β and β-catenin [104]. Similarly, PRKN is related to the ubiquitination of β-catenin, playing a direct role in the modulation of this pathway [105]. The relevance of such regulation has prompted some researchers to propose the pharmacological modulation of Wnt signalling as a relevant target in PD [106]. Complimentary to these well-established effects, Wnt signalling has also been linked to modulation and crosstalk within the inflammatory cascade.

4.2. Wnt signalling and the inflammatory pathway

Although it could be considered circumstantial, the inflammatory status and Wnt signalling are inversely correlated during the ageing process; in other words, while the pro-inflammatory status increases with age, Wnt signalling decreases. Of course, additional signalling pathways are impaired during ageing; however, the fact that Wnt is able to modulate the NF-kB pathway strongly suggests that this particular pathway has a direct impact on the immune/inflammatory response observed during the ageing process. Moreover, it should be considered that even when it is well accepted that canonical Wnt signalling has anti-inflammatory activity and the non-canonical pathway exerts a pro-inflammatory effect, these opposing functions can be carried out by the same ligand, such as Wnt5a [21, 101]. This latter finding also suggests that depending on the physiological or pathological status of the biological system, Wnt components can exert different modulatory effects to contribute to the maintenance of system balance. In contrast, inflammation can also modulate Wnt activity. In this regard, TLR activation can downregulate the canonical Wnt signalling pathway. While TLR4 causes the blockade of the Fz-LRP5/6 complex [107], MyD88-mediated TLR activity activates nemo-like kinase (NLK), which interacts with the nuclear β-catenin-TCF/Lef complex. Similarly, MyD88-independent TLR signalling activates IKKe/TBK1, which can directly phosphorylate Akt, leading to GSK3β inhibition and blocking the activity of the β-catenin destruction complex [108–111].

Although evidence demonstrates a close relationship between Wnt signalling and the inflammatory process, our knowledge regarding this issue remains limited. Moreover, the already proven involvement and the critical role that Wnt signalling seems to play in different aspects of physiological and pathological cellular mechanisms certainly indicate that this pathway needs to be investigated deeply to properly assess the effects of finely modulating Wnt signalling, including its potentially beneficial effects in the context of the inflammatory response. In this regard, part of our work suggests that lithium and andrographolide, both well-established canonical Wnt agonists that act via GSK3β inhibition, can play a relevant role not only under pathological conditions but also as exogenous support of a healthy ageing process by reducing several markers of unhealthy conditions, including neuroinflammation [112].

5. Final considerations

According to the available evidence, ageing constitutes a vulnerable stage for cell fate mainly because of the delicate balance of several molecular conditions. Under these conditions, any additional challenge to any homeostatic system can trigger the breakdown of such equilibrium, leading to the manifestation of pathological processes, such as neurodegenerative disorders. AD and PD, the first and second most prevalent age-related diseases, can be favoured by a spontaneous imbalance in the homeostatic system and, once initiated, further contribute to increasing the homeostatic imbalance. A complex network of molecular alterations, organelle dysfunction and cellular signalling, among others, increases the difficulty of properly addressing the cloudy edge between healthy ageing, pathological ageing and age-related disorders. However, neuroinflammation and the perpetuation of a chronic pro-inflammatory status have emerged as a central axis connecting all these conditions. Although our knowledge regarding the inflammatory process has increased during years, the intricate molecular network that drives the final inflammatory response is still incomplete. In this regard, Wnt signalling, which has been demonstrated to be a relevant player in ageing and age-related disorders, such as AD and PD, should also be considered among the potentially relevant molecular pathways that could be involved in the modulation of the inflammatory process. Moreover, the still limited information regarding the Wnt-inflammatory response crosstalk already suggests interesting potentialities of an anti-inflammatory intervention based on the modulation of Wnt signalling. On the other hand, based on our research and considering the age-related changes in Wnt activity, it is possible to suggest that Wnt signalling can also be an interesting target to support physiological ageing.

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