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Chapter

The Role of Inflammation in Amyloid Diseases

Estefania P. Azevedo and Debora Foguel

Abstract

Amyloid diseases are characterized by the abnormal accumulation of proteinaceous aggregates (amyloid fibrils or plaques) in tissues and organs. This class of diseases is also characterized by the presence of inflammation. Amyloid fibrils arise from the partial denaturing and unfolding of native proteins. The accumulation of amyloid fibrils causes tissue damage and elicits local and nonlocal immune cell infiltration into tissue and proinflammatory cytokine production. Moreover, these conditions fuel a vicious cycle that can increase amyloid production and create an environment of chronic inflammation. A chronically inflamed tissue rapidly deteriorates and loses its function. In this chapter, we will discuss important data gathered over the years describing the role of inflammation in amyloid diseases. We will describe how inflammation begins and how it affects disease progression for major amyloid diseases, such as Alzheimer's disease (AD) and hereditary TTR amyloidosis (hATTR). Lastly, we will discuss the recent advancements in treatments for amyloid diseases and how they address inflammation in affected patients.

Keywords: amyloid diseases, neutrophils, proteases, fibrils, inflammation

1. Introduction

In 1849, the term "amyloid" was first introduced by Matthias Schleiden to describe a starch-like material identified by an iodine-sulfuric acid staining of plant tissues [1]. Later in 1854, Rudolph Virchow observed similar deposits in human nervous tissue that reacted in an analogous manner as the deposits in plants after the addition of Schleiden's iodine-sulfuric acid stain [1]. With the advance in technological power and the advent of microscopy, researchers found that the starch-like deposits found in the diseased tissues of humans were made of proteinaceous structures that were organized as fibrils (termed "amyloid fibrils") and coated with carbohydrates, hence the reaction to iodine-sulfuric acid stains [1]. More than 40 pathologies are part of the family of diseases characterized as "Amyloid Diseases" [2]. The criteria that allow such characterization rely on the fact that these pathologies contain a very specific hallmark: the accumulation of amyloid fibrils in cells, tissues and/or organs. Fibrils are formed after native proteins partly unfold and aggregate into oligomers or amorphous aggregates that later organize themselves into mature, β-sheet-rich fibrillar structures [2]. On a molecular level, amyloid fibrils extracted from different patients can be indistinguishable from each other [2]. These structures can be formed outside the cell or inside the cell [2], and when they accumulate, they cause cellular damage or mechanical damage (if accumulating in between or on top of tissues).

For decades, scientists believed that amyloid fibrils were stable and inert, and the end result of a nontoxic natural pathway that serves to scavenge and store highly reactive and toxic oligomeric intermediates formed during the process of protein folding [3–5]. The reactive hydrophobic residues found exposed in oligomeric intermediates are hidden in mature amyloid fibrils, thus unable to react with important cellular components [6]. Although the latter is true about amyloid fibrils, research in the last two decades shows that these structures are neither inert nor nontoxic [5, 7]. When extracellular, amyloid fibrils are readily identified by the host immune system, mainly by macrophages or neutrophils [8–10]. These immune cells have receptors that recognize and bind to the amyloid fibrils and intermediates, activating a signaling cascade that results in the production of proinflammatory molecules [8–10]. In this chapter, we will review the inflammatory component of some clinically important amyloid diseases, such as Alzheimer's disease (AD) and familial amyloid pathologies, such as hereditary TTR amyloidosis (hATTR or familial amyloid polyneuropathy—FAP). We will also discuss how inflammatory cells contribute to disease progression by causing bystander damage to tissues or by enhancing protein aggregation, in the case of AA amyloidosis. Finally, we will provide the recent therapeutic approaches based on immune regulatory strategies for these diseases.

2. Inflammation in amyloid diseases

Inflammation is the term given to a form of immune defense that is widespread and requires a complex network of immune effector mechanisms to address tissue dysfunction or injury. The notion that inflammation is involved in amyloid pathogenesis was first suggested in the 1970s in two reports on serum amyloid A (SAA) [11, 12]. Nowadays, it is known that this particular amyloidogenic protein expression is regulated by IL-6, an inflammatory cytokine, which results in increased levels of SAA [13]. Hyperexpression of SAA for long periods of time results in amyloid formation and deposition in tissue, characterizing amyloid A (AA) amyloidosis [13]. This particular type of amyloidosis occurs in chronic inflammation conditions, such as autoimmune diseases or cancer [13]. With the exception of inflammation-induced amyloidosis, such as AA amyloidosis, the role of inflammation in most amyloid diseases is a more recent concept that emerged in the late 1980s with the observation of microglia, a brain immune cell, found near amyloid plaques in postmortem brain tissue from Alzheimer's disease (AD) patients [14–16]. After these first observations, more evidence on the involvement of inflammatory mechanism in amyloid pathogenesis has emerged.

2.1 Alzheimer's disease (AD)

Alzheimer's disease (AD) is known as the most common neurodegenerative disease worldwide. It afflicts over 40 million people in the world, and because aging is the major risk factor for developing AD, its incidence will likely increase in the future as medical advances lead to increasing life span [17]. Although there is no definite known causative agent, most scientists agree that amyloid-β peptide (Aβ) is an important factor leading to AD [18]. Aβ is highly amyloidogenic, meaning that it has great potential to aggregate in solution [18]. Aβ is a small peptide ranging from 25 to 42 amino acids [18]. Extracellular aggregates of Aβ are the main protein present in amyloid plaques, a hallmark of AD [18]. Moreover, a small fraction of AD patients is diagnosed with familial AD, which is known to be the result of an infrequently inherited autosomal dominant mutation in one of the three genes

involved with the production of Aβ: the amyloid precursor protein (APP) gene, presenilin 1 (PSEN1), and presenilin 2 (PSEN2) [19]. The first findings pointing to a possible involvement of inflammatory mechanisms emerged around 1980 when scientists reported reactive microglia and astrocytes surrounding amyloid plaques of AD patients [14–16]. Nowadays, after years of research, inflammation is known to be implicated in AD by having a role in neuronal damage [20], Aβ generation [21], increased hyperphosphorylation of tau protein [22] (another hallmark of AD), and cognitive impairment [23]. In this part of the chapter, we will be focusing on summarizing the role of microglia in the progression of AD.

2.1.1 Role of microglia in AD

Microglia are the immune cells of the brain. They derive from myeloid precursors which migrate into the brain during early embryonic development and play a major role in maintaining a healthy environment in the brain [24, 25]. Microglia use their surface receptors to constantly scan the central nervous system (CNS) for microbes or other damaging molecules [26]. When activated by a stimulus, microglia mediate innate and adaptive immune responses or perform various functions in response to CNS disease or injury [26]. Microglia are of great importance for brain homeostasis, but uncontrolled or overactivated microglia can also contribute to brain diseases, such as AD.

Years of research is allowing deeper understanding of how microglia contribute to AD. Microglia produce inflammatory mediators, such as TNF-α [26], that can have a detrimental role when overproduced for long periods of time. Microglia are able to produce large quantities of TNF-α upon exposure to fibrillar and oligomeric Aβ [23, 27]. TNF-α is increased in the serum and CSF of AD patients and has additionally been detected in amyloid plaques [28–32]. Inhibiting TNF-α production with the use of unspecific anti-inflammatory compounds, such as minocycline, or a specific neutralizing TNF-α antibody, (infliximab) results in downregulated inflammatory pathways (e.g., MAPK, AKT, and NF-κB) and abrogates cognitive deficits in mice [23, 33]. It has been shown that fibrillar and oligomeric Aβ can induce production of not only TNF-α but also other important inflammatory cytokines in microglia by binding and activating several receptors [23, 34]. This suggests the existence of a universal epitope found in aggregated material and a nonspecific response to amyloids. Also supporting this idea is the fact that two generic, widely used, conformation-specific antibodies have been generated (A11 and OC antibodies) that recognize mutually exclusive structural epitopes in a range of amyloid-forming proteins, including Aβ, independently of any primary amino acid sequence similarities. A11 antibodies recognize anti-parallel β-sheet structures found in intermediate states, and OC antibodies detect parallel β-sheets found in mature amyloid fibrils [35]. Inflammation is a downstream consequence of aggregated Aβ binding to receptors such as TLR-4 (toll-like receptor 4), RAGE (receptor for advanced glycation end products), CD36 [23, 36, 37], etc. It is important to note that some of these receptors are also able to recognize other aggregated non-Aβ materials [38]. Interestingly, these receptors are not only present in microglia, but some are also present in endothelial cells and neurons [39]. This suggests that the role of Aβ in AD is very complex.

Some receptors that primarily bind monomeric Aβ are not involved in pathological, inflammatory processes. Receptors such as LRP1 (low-density lipoprotein receptor-related protein 1), PrPc (cellular prion protein), and PICALM (phosphatidylinositol-binding clathrin assembly protein) are able to bind monomeric Aβ and are thought to be involved in Aβ clearance, decreasing the Aβ burden and plaque formation in the brain [40]. Moreover, mutations in PICALM, which is a gene

that encodes a clathrin assembly protein and thus is involved in endocytosis, have been shown to be a risk factor for developing late-onset AD [41]. More convincing evidence of the significant role of neuroinflammation in AD is found in recent genome-wide association studies (GWAS). These studies have identified more than 20 gene variants as risk factors for developing late-onset AD. These disease-modifying genes include genes involved in both innate and adaptive immune system responses: *CR1*, *CLU*, *CD33*, *MS4A, ABCA7 EPHA1, TREM2,* and *HLA-DRB5/HLA-DRB1* [41, 42]. It is interesting to note that all of these genes are present in microglia cells as well [41]. It is thought that these genes can change microglia function and increase the risk of AD.

2.1.2 Role of peripheral inflammation in AD

An emerging concept based on recent work is that peripheral inflammation, in addition to local, brain inflammation, also affects AD pathogenesis. Studies suggest that myeloid cells, such as neutrophils, can enter the brain and may also involve in Aβ clearance [10, 43]. Neutrophils can recognize fibrillar Aβ and produce *in vitro* and *in vivo* extracellular traps (NETs; a defense mechanism that results in neutrophil cell death) [10, 43]. Extracellular traps are protein and DNA-made meshes that can immobilize Aβ particles, degrade fibrillar amyloids, but are known to modulate other immune system effector mechanisms as well [44].

Acute systemic inflammation, caused by bacterial infection, exacerbates AD pathology [45], and chronic systemic inflammation, occurring in diseases such as rheumatoid arthritis (RA), depression, and obesity, has also been reported to modify the amyloid phenotype of AD mice and is considered common co-morbid states of AD patients. In autoimmune disease, chronic inflammation can increase the risk of developing AD. Patients with the autoimmune disease Sjögren's syndrome (SS) are twice as likely to develop AD [46]. In RA, it has been shown that anti-TNF-α therapy has a protective effect on dementia [47]. In the case of depression, Aβ accumulation in AD mouse models induces depressive-like behavior, which is dependent on inflammation [23]. Inflammatory cytokine production reduces serotonin levels and contributes to behavioral changes in mice with AD [23]. Again, this can be prevented by anti-TNF-α therapy [23]. Obesity is a known comorbidity of AD and a low-grade chronic inflammatory disease. In humans and AD mouse models, cafeteria diet consumption and a higher BMI are known to accelerate AD pathology [48, 49]. For example, in humans, for every 1.0 increase in BMI at age 70 years, AD risk increased by 36% in female patients [49].

In an attempt to cure AD, active immunization against Aβ was performed in mice and humans [50, 51]. Studies reported that immunization had a therapeutic effect on mouse models of AD [50–52]. Unfortunately, clinical Aβ vaccination trials have been interrupted due to the development of meningoencephalitis in 6% of the patients, likely involving the appearance of pro-inflammatory macrophages, CD4+ and CD8+ T cells [50]. As well as myeloid cells, T cells can enter the brain. There are myriads of T-cell subtypes surveilling the CSF and the meningeal membranes [53], and they can enter the brain parenchyma upon cell injury [53]. It is not only brain-local T cells that react to Aβ but also blood T cells have been shown to have hyperreactivity to the Aβ peptide [54], specifically to epitopes within the residues 15–42 [54]. This evidence together suggests that the immune system and inflammation play significant roles in AD: not only helping with homeostatic Aβ clearance and preventing AD plaque formation but also by contributing to cell injury. Unfortunately, to date, tackling the immune system to prevent AD has yet to prove clinically effective.

2.2 Hereditary ATTR (hATTR) amyloidosis

Transthyretin (TTR) is a 55-kDa tetrameric protein expressed and secreted mainly not only by the liver, but also by the choroid plexus in the brain [55]. This protein received this specific name due to its function: once in the plasma or in the cerebrospinal fluid, TTR acts as a retinol-binding protein and thyroxine transporter across the body [55]. More than 100 point mutations in the TTR gene have been described worldwide and most of them culminate in the production of abnormal protein with a high thermodynamic instability compared to its wild-type counterpart [55]. Only a handful of mutations are not pathogenic, such as the T119M mutation [56]. The pathogenic V30M variant is the most common mutation affecting a large population of people worldwide and results in the accumulation of TTR in various tissues, such as cardiac and nervous tissue [57]. Most TTR mutations have a high propensity to aggregate under denaturing and even physiological conditions [58], forming amyloid fibrils that deposit in various tissues and organs [58]. For decades, most physicians and pathologists still regard hATTR amyloidosis as a disease without an inflammatory component, since most biopsies and *ex vivo* analysis showed no leukocyte infiltration [59]. However, with the appearance of new data in the last decade, hATTR amyloidosis is now being recognized as a disease with an important inflammatory component. Moreover, TTR amyloid fibrils are similar in structure to other amyloid fibrils and thus should induce similar inflammatory responses. One of the most common types of hATTR amyloidosis is known as familial amyloid polyneuropathy (FAP). FAP is an autosomal dominant hereditary disease characterized by the accumulation of amyloid fibrils in peripheral nerves, the gastrointestinal tract, and the heart [59]. This disease has three discernable stages: FAP 1 = unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs; FAP 2 = assistance with ambulation required; mostly moderate impairment progression to the lower limbs, upper limbs, and trunk; FAP 3 = wheelchair-bound or bedridden; severe sensory, motor, and autonomic involvement of all limbs. This disease, as most amyloidosis, is incurable and results in death [59].

The diagnosis of FAP is challenging, often relying on genetic screening to identify TTR mutations as well as on the identification of Congo red-positive amyloid deposits in biopsies. These biopsies are generally invasive, and tissue is usually taken from the sural nerve, abdominal fat, or salivary glands [59]. The main *go-to* treatment for FAP is liver transplantation (LT), since the liver is the major organ of TTR production. Unfortunately, LT presents mortality risks, and it is not available to all patients [60]. More recently, two new drug-based treatments have been FDA approved. One of these treatments use a new drug (Tafamidis) that works by stabilizing the TTR protein that is available in several countries showing effective results in controlling disease progression [61]. The other, just recently approved by the FDA, uses antisense oligonucleotides (ASOs) to target TTR production in the liver directly, decreasing the amount of TTR in the plasma, thus reducing protein aggregation [62].

Since the first study in 2001, the new concept that inflammation may play a role in the pathogenesis of FAP has emerged. Sousa and colleagues showed the presence of proinflammatory markers such as TNF-α and IL-1β in biopsies of FAP patients [63, 64]. Interestingly, the levels of proinflammatory and oxidative markers in *ex vivo* tissue positively correlate with the scoring stage proposed by Coutinho and colleagues in FAP patients, which is an index used to discriminate disease progression [65]. In addition, their study also showed the participation of the receptor RAGE, which can also bind Aβ fibrils, in the recognition of TTR amyloid fibrils [63]. In this first study, the authors suggest that Schwann cells, which are cells

that myelinate peripheral nerves, were responsible for the cytokine production observed in the neural tissue. A few years later, the presence of neutrophil-derived proteins in TTR amyloid deposits was described [66]. Proteins such as lipocalin and metalloproteinases were found together with TTR deposits in FAP patients [66]. The authors suggest that the sural nerve itself is the possible tissue producing these proteins for extracellular matrix remodeling and might be an effort to degrade amyloid fibrils deposited around them. Interestingly, a forgotten report in 1986 already reported the presence of neutrophil-derived proteins in amyloid-containing tissue [67]. The report in 1986 describes the presence of elastase, a neutrophil's granule enzyme, in amyloid-containing tissue from patients diagnosed with AA amyloidosis, primary amyloidosis caused by immunoglobulin light-chain aggregation and hATTR amyloidosis [67]. Notably, intact neutrophils were not found, which confirms the most pathologist reports of FAP tissues not having leukocyte infiltration. But how intracellular components from neutrophils appeared in amyloid-containing tissue? Azevedo and colleagues reported in 2012 that a common epitope found in amyloid fibrils arising from different proteins, one of them being TTR, are able to activate neutrophils and induce elastase secretion in the form of extracellular traps [10]. These structures, called neutrophil extracellular traps (NETs), represent an important strategy to immobilize and kill invading microorganisms or in this case, aggregated proteins. The NET scaffold consists of DNA fibers associated with various granule proteins, one of them being elastase [10]. These elastase and DNA-traps accumulate in amyloid tissue and thus could explain why elastase and neutrophil-derived proteins are found around amyloid tissues in FAP patients [10]. This immune response could also be an effort to eliminate amyloid fibrils or oligomers from the affected tissue. In 2012, another important report by Buxbaum and colleagues used an animal model of FAP to study the disease progression in mice [68]. The study showed the increased levels of inflammation-related transcripts in both liver and heart of transgenic mice, strengthening the concept that inflammation might play an important role in FAP progression [68]. Additionally, Kurian and colleagues have observed sex-specific changes in blood cell gene expression in FAP patients, suggesting that inflammatory gene markers in circulating blood cells might be influenced by sexual dimorphisms [69]. More recently, new evidence shows the presence of elevated levels of IL-6 in FAP carriers that may be produced by myeloid cells and T cells [70].

These studies altogether suggest that inflammation in FAP consists of two different phases. One phase in which inflammation possibly begins at the moment of TTR production in the liver. The synthesis and abnormal folding process of the mutated and unstable TTR in the liver requires a high energetic state and thus, may cause endoplasmic reticulum (ER) stress and the activation of the liver unfolding protein response (UPR). ER stress and the activation of UPR in liver were shown to cause pro-inflammatory cytokines production, such as IL-6 [71, 72]. IL-6 is known to increase the production of other proinflammatory intermediates and could enhance inflammation levels locally in the liver by activating liver-associated macrophages as seen in other nonamyloid diseases [73, 74]. It is ultimately important to understand whether the liver plays an important role in the inflammation observed in FAP patients due to the fact that most of these patients undergo domino liver transplant. In this procedure, a liver failure patient receives a liver from a FAP patient. However, a five-year study described that 35% of patients that underwent domino liver transplantation presented FAP symptoms earlier than donor FAP patients [75]. These data indicate that FAP patients may have altered liver capacity and a low-grade chronic inflammation, decreasing the success of liver transplants. The second phase occurs after unstable TTR reaches the bloodstream and aggregation starts. TTR oligomers have been found in blood from FAP patients [76] and could

elicit the production of various inflammatory cascades in circulating leukocytes and T cells. Amyloid oligomers are formed before fibril deposition and have been shown to be toxic to cells [77] and elicit inflammation when presented to immune cells [23]. Small, toxic oligomers can also be produced in situ after the cleavage of mature fibrils through the action of local proteases, such as elastase and metalloproteinase-9 [10, 66].

So far, in FAP patients and hATTR mouse models as well as in vitro, TTR fibrils are able to elicit inflammation and activate a myriad of cell types. In a broader clinical context, the underlying inflammation that begins in asymptomatic patients and continues chronically might be important for the development of FAP-associated symptoms. Patients with FAP present symptoms other than neuropathy, such as gastrointestinal symptoms, cachexia, malnutrition, diarrhea, and others [59]. Inflammatory molecules are known to change neuroendocrine pathways leading to anorexia and thus cachexia in FAP patients. These new data point to an explanation for a lot of unknowns concerning the pathogenesis of FAP. Additionally, understanding the role of inflammation in hATTR will help improve the quality of life and disease management in affected patients. There are currently no studies showing if inflammation can increase the risk of developing hATTR. However, it is possible that an inflammatory environment could decrease liver function and predispose an individual for the production of misfolded proteins, such as TTR.

2.3 Other amyloid diseases

Although recent papers have confirmed that amyloid fibrils present polymorphisms in topology, amyloids still possess an unchangeable structural fingerprint that is shared across species [78]. A lot of different proteins are able to form amyloid fibrils and not all amyloids are pathogenic. Various hormones are present in amyloid form in the pituitary gland [79], and melanocytes possess amyloids, which contribute to melanin formation [80], etc. What makes an amyloid pathogenic or not is still unclear. However, amyloids also possess another universal characteristic: they are able to activate the immune system and induce inflammation. This suggests that inflammation may be an important component of many other amyloid diseases. Indeed, inflammation has been described in many other amyloid diseases. In Parkinson's disease (PD), the involvement of inflammation in the disease process is supported by data showing the infiltration of activated microglia and T cells in post-mortem PD brains [81, 82] Additionally, there is accumulation of proinflammatory cytokines such as TNF-α, IFN-γ, and IL-6 IL-1β in the brain and cerebrospinal fluid of PD patients [83, 84]. The PD culprit protein, α-synuclein, is able to bind to several immune receptors and elicits *in vitro* and *in vivo* inflammatory response [85]. Local inflammation has been thoroughly reported for PD patients, mainly derived from activated microglia [82, 85]. Protein aggregation in PD extends well beyond the CNS and also affects peripheral autonomic neuronal circuits, such as the enteric nervous system [86]. Gut inflammation has been recently reported in PD and is thought to be an important component of the disease [86].

Prion disease is another widely studied amyloid disease and is also known as Creutzfeldt-Jakob disease, fatal insomnia, spongiform encephalopathy, and Kuru. Prion diseases are rare, progressive neurodegenerative disorders that affect both humans and animals [87]. They are caused by the aggregation of PrPc (cellular prion protein) into transmissible, pathogenic prions [87]. These diseases are accompanied by long incubation periods and brain changes associated with neuronal loss [87]. Identifying a role of inflammation in these diseases is rather recent and begun with studies showing that the pathological hallmarks of the prion diseases are associated with the presence of activated astrocytes and microglia [88]. CD8+ T cells are

also present in prion-affected brains and usually are found near activated microglia and prion amyloid plaques [89]. As inflammation progresses, inflammatory cytokines are also detected in prion-containing brains [88], and these are thought to play an important role in behavioral changes and neuronal loss observed in affected mice. And this is yet another example of inflammation being widely present and contributing to pathogenesis in an amyloid disease which was first thought to not have an inflammatory component.

3. What is in store for the future: Therapies for amyloid diseases

Most amyloid diseases are still incurable. However, most of them can be managed using palliative care and drugs to decrease symptoms and extend the patients' lives. In AD, efforts are concentrated in decreasing symptoms such as cognitive deficits [90]. Currently, there are five FDA-approved drugs to treat cognitive symptoms associated with AD. These drugs are basically acting on two different neurotransmitter systems in the brain: the cholinergic system and the glutamatergic system [90]. They act by blocking glutamate receptors and inhibiting cholinesterase activity, thus these drugs, when combined, can decrease excitotoxicity induced by an overload of glutamate in the synapse and making acetylcholine more available for a healthy synaptic transmission [90]. While in theory, and as seen in mouse models of AD, these drugs seem effective, in humans they work to certain extent decreasing the symptoms. Although these drugs can temporarily decrease symptoms, they are not able to stop the progression of AD, as they do not address amyloid accumulation [90]. Although great results were seen in mouse models, in AD patients, clinical trial using nonsteroidal anti-inflammatory drugs (NSAID) were unsuccessful to prevent or treat the disease, but these drugs only account for a small part of inflammatory pathways dependent on cyclooxygenases (COX) and have diverse side effects. For PD, treatment using drugs is aimed at enhancing cholinergic and dopaminergic transmissions and hence decreasing motor and gut-related symptoms, such as tremors and constipation [91]. Deep-brain stimulation is a surgical treatment available for PD and can also decrease motor symptoms [91]. Most treatments, as the ones described above, are aimed at treating the consequence of amyloid accumulation rather than treating the amyloid accumulation itself or the inflammatory components of these many amyloid diseases.

For the hATTR diseases, two FDA-approved drugs have been developed to prevent amyloid accumulation in patients: tafamidis, a drug that stabilizes TTR and decreases TTR aggregation and antisense oligonucleotides against TTR, a drug that aims in reducing TTR production in the liver [61, 62]. In structure, tafamidis resembles most NSAID, and hence, it does not have any NSAID activity [92]. Notably, many other NSAID drugs also bind to TTR, stabilizing it [93]. However, many have not been to clinical trials at all or have not been successful in clinical trials because chronic use of NSAIDs is not indicated for patients with liver, renal, and heart problems [94], which are part of the symptoms affecting FAP patients. NSAIDs have also been used for treating other amyloid diseases, such as AD and PD, but again without success [95, 96]. Indeed, many AD and PD patients are older individuals that also possess additional conditions that exclude them from the chronic use of NSAIDs. The use of immunotherapies, especially for AD, has been thought to be an effective approach to treating the disease, but clinical trials have shown that autoimmune meningoencephalitis develops in a significant number of patients undergoing immunotherapy [50]. Usually these treatments aim to use

antibodies to neutralize the culprit of the disease, in the case of AD, the Aβ peptide [50]. Unfortunately, the autoimmune response, consisting of hyperreactive T cells, of patients has prevented the clinical trials from continuing further. Researchers are still investigating immunotherapies as a way to treat AD and managing the T cell response.

The use of antisense nucleotides (ASOs) for successfully decreasing the amount of native protein in the body remains the most effective therapy and maybe the path to cure amyloid diseases. ASOs have already been shown to be effective in hATTR disease [62], without eliciting any further autoimmune inflammatory response in patients receiving the therapy. There is growing interest in using ASOs in AD and PD, since many proteins that cause amyloid diseases have unknown or redundant physiological function [2]. This suggests that decreasing the levels of native, healthy protein in individuals may not cause problems for most bodily functions. By reducing the levels of native protein, ASOs ultimately decrease amyloid formation and accumulation and finally, all the immune responses that might come with unstable protein synthesis, aggregation, and amyloid deposition in tissue.

4. Conclusion

Amyloid diseases have been described in humans and animals since the 1800s. This family of diseases has one defining characteristic: the presence of extracellular proteinaceous aggregates (amyloid fibrils or plaques) in tissues and organs. These amyloid fibrils arise from the unfolding of native protein, which vary according to the disease (for example, Aβ peptide in AD). Another common characteristic of amyloid diseases is the installment of inflammation during and after amyloid formation. Amyloid fibrils and tissue damage elicit local and nonlocal immune cell infiltration into tissue and proinflammatory cytokine production. Together, these fuel a vicious cycle that can increase amyloid production, as seen in AA amyloidosis, and create an environment of chronic inflammation. A chronically inflamed tissue, as seen in autoimmune diseases, rapidly loose function and deteriorates. This is especially true for the nervous system, a delicate tissue in which self-repair is almost impossible. As most amyloid diseases affect the CNS, and inflammation is a fundamental component of amyloid disease, studying inflammation in the CNS is imperative to our understanding of how to treat amyloid disease. Many current treatments focus on the consequences of amyloid accumulation and fail to address the basic underlying causes. The use of ASOs brings promise of improvements in amyloid disease therapeutics and fortunately is growing as an important tool used in disease therapy. Recognizing that inflammation plays a significant role in amyloid disease is essential to understand the pathogenesis of amyloidosis and important for developing new targeted treatments in an era of growing demand.

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Conflict of interest

We report no conflict of interest.

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