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Review

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Abstract: Many of the potential immune therapeutic targets are similarly affected in adult-onset neurodegenerative diseases such as Alzheimer's (AD) disease, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and frontotemporal dementia (FTD), but also in a seemingly distinct Niemann-Pick type C disease with primarily juvenile-onset. This strongly argues for an overlap in pathogenic mechanisms. The commonly researched immune targets include various immune cell subsets such as microglia, peripheral macrophages, or regulatory T cells (Tregs), the complement system, and other soluble factors. In this review, we will compare these neurodegenerative diseases from a clinical point of view and point out the common pathways and mechanisms of protein aggregation, neurodegeneration and/or neuroinflammation that could potentially lead to shared treatment strategies. We also describe the common therapeutic approaches in treating the immune dysfunctions in these disorders, moving from immunization to microbiome regulation and stem cell treatment.

Keywords: Alzheimer's disease; Parkinson's disease; Niemann-Pick type C disease; neurodegeneration; neuroinflammation; immunomodulatory therapies; rare diseases

1. Introduction

Neurodegenerative diseases (NDDs) share several common mechanisms, most prominent of which is neuroinflammation [1,2]. Neuroinflammation, evident as activation of microglia and astrocytes, which results in increased proinflammatory cytokine and reactive oxygen species generation, is one of the main mechanisms that causes neuronal death. Although it was traditionally

considered to be almost exclusively a late step in disease pathogenesis, multiple lines of evidence have recently shown that it could be an early step as well {reviewed in [3,4]. This review will focus on overlapping neuroimmune mechanisms and potential shared therapeutic targets in several key NDDs. In a recent review article, we have already discussed the proposed immune imbalance underpinning amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) [5], which we will here extend to two other late-onset NDDs - Alzheimer's disease (AD) and Parkinson's disease (PD), and an early onset Niemann-Pick type C disease (NPC), due to its extensive and intriguing overlap with AD. We aim to depict common targets that could lead to faster translation and shared therapies.

1.1. Brief overview of distinct and overlapping clinical features in neurodegenerative diseases

AD is a progressive degenerative disease of the brain and the most common cause of dementia among elderly people, accounting for at least two-thirds of all dementia cases [6]. AD is defined as a progressive decline in cognitive functions, typically beginning with memory impairment, and a characteristic change in personality and executive functions. FTD represents a group of disorders considered to be clinically and pathologically distinct from AD, although FTD may be mistaken for AD in the early clinical stages [7,8]. The FTD clinically presents as either behavioural or aphasic variants, reflecting the topography of the underlying synaptic and neuronal loss [7,9,10]. The most common, behavioural or frontal variant of FTD is associated with disinhibition, impulsivity, apathy, and loss of insight that disturbs social component and typically is accompanied by marked frontal lobe atrophy. The aphasic variant is further divided into two subtypes: the non-fluent form (primary progressive aphasia), with hesitant diminished speech output for which left frontotemporal lobe involvement is characteristic; and the fluent form (semantic dementia) with severe naming and word comprehension and visual recognition deficit (agnosia) for faces and objects that involves bilateral anterior temporal lobes. Therefore, the clinical phenotype of FTD may overlap with AD in memory and executive dysfunction, but is distinct in terms of behavioural problems and language difficulties. ALS and FTD are related clinical phenotypes, which are characterized by decline in motor, cognitive and behavioural function, and short survival. ALS is the most common adult-onset motor neuron disease, characterized by the progressive, irreversible motor neuron loss leading to denervation atrophy of muscles and death by respiratory failure. However, it is increasingly recognized that ALS is a multisystem disorder in which other non-motor (cognitive and behavioural) impairments can be observed, whereas, on the other side, FTD can be associated to signs of motor neuron disease (FTD-MND) [11].

Niemann-Pick type C disease (NPC) is an autosomal recessive neurovisceral lipid storage disorder, characterized by liver dysfunction and progressive neurodegeneration [12,13]. It is characterized by a highly heterogenous and variable clinical phenotype, from a rapidly progressing neonatal form to an adult-onset chronic neurodegenerative condition. The neuropathological features of NPC disease include loss of Purkinje neurons in the cerebellum, hyperphosphorylation of tau and widespread occurrence of neurofibrillary tangles (NFTs), the presence of dendritic and axonal abnormalities, and profound neuroinflammation (activated astrocytes and microglia) [14–17]. While hepatosplenomegaly together with motor problems is initially observed in neonatal and infantile forms along with other symptoms, the juvenile and adult forms of NPC are typically manifested by a variety of progressive neurological and/or psychiatric symptoms including ataxia, dystonia, hearing loss, epileptic seizures, dysarthria, dysphagia, cognitive impairment, and dementia. Indeed, these NPC patients display an apolipoprotein E ε4-dependent accumulation of amyloid-ß peptides (Aß) into diffuse Aß plaques as well as widespread occurrence of NFTs in their brains [14–16] the two characteristic features of AD. For this reason, NPC disease is often called juvenile AD.

PD is the second most common NDD after AD, where the cardinal motor features include akinesia/bradykinesia, postural instability, and resting tremor. Here, it should be noted that while many of the motor symptoms arise from the loss of dopamine neurons in the substantia nigra, neuropathology occurs systemically and elsewhere in the brain, resulting in an array of additional motor and nonmotor symptoms; notably prominent are constipation (damage to enteric nervous

system), mental health effects, and REM behaviour disorder, and loss of cognitive functions (can be especially prominent at the late disease stages) [18,19]. The affected functions vary from defects in performing executive tasks, visual perception, attention, memory loss and dementia. The cognitive impairment has been reported in up to 90% of PD cases, with dementia cases comprising up to 30% of cases, thus making cognitive manifestation one of the most important non-motor aspects of the disease. Overall, it has become clear that NDDs often show a broadly mixed pathologies and that many patients are now considered to belong to a disease spectrum rather than to a discrete NDD.

The importance of all of these overlapping features of NDDs should be more appreciated especially in cohort characterization for clinical studies, development of the future therapies as well as in biomarker design and its monitoring, with the ultimate goal towards precision/personal medicine.

2. Overlapping pathogenic mechanisms in neurodegenerative diseases

The pathogenic mechanisms implicated in NDDs are not linked to individual clinical entities. In contrast, NDD pathogenesis shows a considerable overlap in protein misfolding and aggregation, defects in endosomal-lysosomal network and clearance of damaged proteins by autophagy or proteasomes, mitochondrial dysfunction and oxidative stress, cellular calcium imbalance, impaired axonal, membrane or nucleocytoplasmic trafficking, DNA damage response and synaptic dysfunction, many of which crosstalk, and are directly or indirectly linked to neuroinflammation and even systemic immune imbalance [19–27]. Most of these mechanisms are also affected by ageing, the most prominent risk factor for adult-onset NDDs, which is in the immune system linked to immunosenescence, with increased activated adaptive immune cells and decreased repertoire of naïve cells, and chronic low-grade inflammation [28,29]. In this chapter we will focus on overlapping proteinopathies and immune imbalance in NDDs, the two features that have recently been tackled for designing and monitoring efficient therapies.

2.1. Overlapping proteinopathies

Thanks to our increased ability of detecting pathological protein species in the brains of patients affected by NDDs, it has been clear since the last decade that overlapping proteinopathies exist throughout the entire spectrum of most NDDs [30]. Notably, Aβ aggregates are commonly present in AD and NPC, tau in AD, NPC and FTD, TDP-43 in ALS and FTD, and α-synuclein (α–syn) in PD [14,31–33]. Less commonly, but by no means as an exception, TDP-43 pathology is found in AD and PD, Aβ in PD and α-syn in AD and FTD. Just to provide some indication of how frequent comorbidities could be in neurodegeneration - it has been estimated that only 20% of all AD cases that occur after the age of 70 can be defined as "pure" AD cases [34]. In most of these cases, the comorbidity occurs between tau pathology and another major actor in NDDs represented by the TDP-43 protein that plays a major role in ALS and FTLD-TDP, as recently reviewed by Riku et al. [35]. The occurrence of comorbidities has substantially changed our view of neurodegeneration processes: from considering AD, PD, ALS, FTD, etc. as distinct and well-defined pathologies to viewing them as a potentially interconnected spectrum of neurodegeneration, where comorbidities may often influence the main pathology and affect both disease progression and duration. When trying to address this new finding, another important question to answer is whether the overlapping pathologies have the same site-specific characteristics compared when they are alone. For both questions, some answers have already been provided with regards to prominent comorbidities. For example, TDP-43 pathology in the AD brains, considerably differs from the primary motor-cortex involvement that is characteristic of this protein in ALS. Rather, TDP-43 pathology in AD brains starts in the amygdala and goes through several stages to finally reach the basal ganglia and middle frontal cortex [36].

Another type of comorbidity that has been studied in the past especially at the mechanistic level is represented by α-syn in brain inclusions of AD patients, that has been recently reviewed by [37,38]. At the mechanistic level, α-syn and tau have been shown to be connected in several ways, with α-syn fibrils being able to promote tau aggregation [39,40]. Taken together, these observations suggest that

protein aggregation comorbidities can play an important role in NDDs, and that their study could be prioritized in future studies to better understand their pathological and clinical connections.

In addition, a careful identification of comorbidities could also be pivotal for the interpretation of clinical trials results. In fact, through the development of appropriate biomarkers, it would be greatly advantageous to start stratifying treated subjects by presence and types of accompanying comorbidities. This action might be able to uncover clinical response variability in some groups as compared to others, potentially "rescuing" treatments that might otherwise fail completely if this factor is not taken into account. For this reason, accurate in vivo comorbidities detection methods are urgently needed for the future of therapeutic research.

2.2. Overlapping immune imbalance

As mentioned above, many pathogenic mechanisms in NDDs are intricately linked to neuroinflammation and systemic immune imbalance. At a cellular level, microglia, the resident macrophages in the brain and spinal cord, are the primary immunocompetent cells in the CNS that have a pleiotropic neurotrophic function [41,42]. In response to protein aggregation and various other neurotoxic conditions, microglia dynamically react in different ways, which range from neuroprotection to neurotoxicity. Similarly, astrocytes, the most abundant CNS glial cells, modify their functional status in pathological conditions [43]. When activated, microglia and astrocytes promote the release of immune mediators, including chemokines and interleukins, that, if persistently elevated, promote the onset and progression of NDDs, becoming potential therapeutic targets [44,45].

Several genes directly affecting immune functions have been linked to ALS and/or FTD, such as *C9ORF72*, *TBK1*, *OPTN*, *CYLD*, *GRN* (reviewed in [3–5,46]). Moreover, as detailed below, genes enriched in microglia have been increasingly implicated in AD pathogenesis over the last decade. It is interesting though, that there is only moderate genetic overlap between NDDs. A recent large GWAS study found evidence for only eleven shared loci in AD, PD and/or ALS, which were potentially linked to genes affecting lysosomal or autophagic functions, neuroinflammation, DNA damage response, and oxidative stress [47]. However, despite such comparably small overlap in individual genes, functions defective across the broad spectrum of NDDs are linked to phagocytosis, lysosomal functions, autophagy, inflammatory signalling, activation of complement and others [48–52]. Many of these functions, including activation of complement, inflammatory signalling, and phagocytosis are beneficial only in a narrow window, and if uncontrolled can lead to various harmful effects, including extensive synaptic pruning and bystander cytotoxicity [51–55]. The harmful effects of these factors are not limited to the CNS, and many lead to systemic immune imbalance. Higher neutrophil counts and blood proinflammatory factors are linked to a higher risk of developing ALS, AD and PD [56–59].

Given that genetics can explain only a small fraction of NDD cases and that most have a complex environmental component, many environmental factors have been researched, such as infectious diseases, microbiome composition, toxins (pesticides and other), most of which affect immune responses. The proposed link between viral infection and NDD has been studied since the Spanish flu of 1918, which was caused by influenza A virus subtype H1N1 [60]. Since then, multiple viruses proposed to increase the risk such as herpes simplex virus 1 (HSV-1) for AD, retroviruses for ALS, and others [61–64] Most recently, similar risk has been found for SARS-Cov2 and is predicted to have a great impact given the large number of affected individuals in the corona virus 19 (COVID-19) pandemic [65]. In perhaps the most comprehensive study thus far, exposure to 45 viruses was linked to NDDs in a Finnish cohort, 22 of which were replicated in an UK cohort [66]. While the large risk effects such as those reported between viral encephalitis and AD were rare, moderately increased risk was very common. Notably, severe cases of influenza and pneumonia were significantly associated with five NDDs (AD, PD, ALS, vascularized and general dementia). Most of the associations were more strongly linked to NDD one year prior to their diagnosis, but some exposures affected the risk up to 15 years prior to the diagnosis. Fittingly, associations with neurotropic viruses were the most common (>80%), and none of the viruses seemed to confer neuroprotection. Similar

associations have been reported for severe systemic bacterial infections in AD, as further discussed below [67]. Overall, this strongly argues that CNS and systemic inflammation is linked to NDDs and that preventive vaccines should be pursued more aggressively, not only to avoid infections, but also their long-term aftermath like NDDs.

The role of the gut microbiome in the pathogenesis of NDDs is of great interest since it has been shown that its composition differs in people afflicted with NDD when compared to the healthy population [68,69]. Changes in relative abundances of different microbial taxa have been shown to factor into neurodegeneration, going as far as to influence the severity of the symptoms of certain diseases, such as in the case of PD, where it has been shown that changes in the relative abundance of various taxa can be correlated, either positively or negatively, with motor and non-motor symptom severity [70]. It has been hypothesized that these effects are achieved, among others, through the gut-brain axis (GBA). GBA is a complex bidirectional system operating between the intestines and the brain, and it has been demonstrated in a number of studies that it could drive neurodegeneration in conditions such as AD and PD [71]. So far, several ways in which this system could operate have been described. These include retrograde axonal transport across the vagal nerve [72], microbial metabolites, such as short-chain fatty acids (SCFA) [72], serotonin-microbiota interaction [73], tryptophan-kynurenine metabolism [74] and immune signalling [75]. Direct evidence for the involvement of the immune system came also from studying *C9ORF72*, the most common genetic risk factor for both ALS and FTD, which acts in autophagy and endolysosomal pathways to suppress inflammation. Indeed, *C9ORF72* has also been shown to suppress microbiota-induced inflammation in mouse models [76]. Therefore, the evidence that the immune signalling linked to microbiota can play an important part in disease pathogenesis is being gathered for many NDDs [77,78].

2.2.1. Immune imbalance in Alzheimer's disease

Recent genome-wide association studies (GWAS) of the late-onset AD (LOAD) have identified risk factors in genes expressed by microglia (*TREM2*, *CD33*, *CR1*, *INPP5D*, *SPI1*, *BIN1*, *PICALM*, *ABCA7*, *SORL1*, *CD2AP* and the *MS4A* gene cluster) or crucial for microglial development and function (*PU.1*) [79–83], suggesting that immune dysfunction and neuroinflammation could drive neurodegeneration rather than being only considered as a (late) consequence of protein aggregation. Microglial dysfunction thus became considered as a major contributor to AD risk [57], challenging the long-standing Aβ hypothesis, which posits that Aβ is the initial disease trigger, while an excessive inflammatory response of microglia is secondary to accumulation of Aβ peptides and Aβ plaque formation [84,85]. Interestingly, several of the above-listed GWAS risk factors are functionally linked to microglial phagocytosis and Aβ clearance [86–89], placing dysfunction of the immune system in the CNS in the centre of AD pathobiology. Although the genesis of disease-associated microglia (DAMs) is a characteristic feature of AD, it is still a matter of debate whether DAMs are "good" or "bad", i.e., whether microglial activation and neuroinflammation is beneficial (neuroprotective) or detrimental (neurotoxic) for disease progression. Notably, single nuclei RNA sequencing (snRNASeq) in AD brains recently showed that distinct microglia profiles are linked to Aβ and tau-associated pathology [90]. On the other hand, chronically altered microglia in AD could compromise not only phagocytosis, but also other physiological functions, including cytokine, chemokine, and growth factor secretion [91,92]. Moreover, APOE ε4 allele, a major genetic risk factor of LOAD [93], has been functionally linked to reduced Aβ clearance [94,95], implying its direct or indirect role in microglial function. Recent snRNA-seq analyses of the frozen AD patients' brains and preclinical models revealed significantly upregulated expression of ApoE in DAMs and not exclusively in astrocytes, as previously assumed [96]supporting an emerging view that microglia are an important contributor to ApoE biology in the CNS [97–100]. In addition to genetic risk factors that link the genesis of LOAD with microglial dysfunction, ageing is another important risk factor that may influence microglial phagocytic capacity and neuroinflammation through epigenetic mechanisms. Indeed, age-dependent accumulation of Aβ in the LOAD patients seems to be associated with age-related decrease in microglial phagocytic capacity [101]. Furthermore, a study using an AD mouse model (APP/PS1) has shown that only young microglia from wild-type mice cleared Aβ plaques, and

that exposure of old microglia to conditioned media of young microglia increased their proliferation and reduced Aβ plaque size [101]. This suggested that microglial dysfunction in AD could be reversible and that the phagocytic ability could be modulated to prevent and/or restrict Aβ accumulation. Lastly, it is now increasingly accepted that infectious diseases may be involved in the aetiology of AD, exemplified by the recent influence of COVID-19 on a spectrum of neurological manifestations [102–104]. Similarly, other severe infections requiring hospitalization have recently shown to increase the risk of dementia [105], further supporting an important role of immune system in the pathogenesis of AD.

2.2.2. Immune imbalance in Niemann-Pick type C disease

It is intriguing that a rare inherited lysosomal and lipid storage disorder Niemann-Pick type C disease (NPC) shares several key features with AD [106] (Figure 1). Among these, neuroinflammation seems to play an early and important role in disease progression, together with neurodegeneration. However, in contrast to the complex genetics of AD, NPC is a monogenic disease caused by mutations in NPC1 or NPC2 genes (95% and 5% of cases, respectively) [106]. These mutations result in dysfunction of cholesterol transport proteins NPC1 or NPC2, accumulation of unesterified cholesterol and other lipids (e.g., glycosphingolipid, sphingomyelin and sphingosine) in late endosomes/lysosomes and their dysfunction [107,108]. The molecular mechanism of neurodegeneration and neuroinflammation in NPC is currently unknown but, although peripheral organs such as liver and spleen are also affected, NPC1 expression restricted to CNS was capable to rescue both neurodegeneration and lethality in NPC1 null mice [109]. Notably, the restoration of NPC1 in neurons only does not fully rescue the phenotype, indicating that NPC1 is functionally important in other CNS cells as well [110–113]. Indeed, NPC1 is ubiquitously expressed throughout the brain with particularly high expression in microglia and oligodendrocytes [114]. It has been generally assumed that neuroinflammation in NPC is secondary to neuronal loss. However, recent findings in NPC1 mice and NPC patients' blood-derived macrophages [114], suggest a possible causative rather than consequential role of neuroinflammation in NPC neuropathology. Notably, NPC microglia proteome changes precede neuronal loss and contribute to neuropathology in a cell autonomous manner. Importantly, lipid accumulation in NPC1-mouse microglia is a consequence of impaired lipid trafficking with a striking accumulation of multivesicular bodies, while lysosomal degradation function seems preserved. Among these, late endosomal/exosomal marker CD63 was the most significantly changed protein at the presymptomatic stage, suggesting that defects within endosomal/lysosomal trafficking and sorting may be among the earliest pathological alterations in NPC microglia. Recently, single cell transcriptomics of the NPC1 mouse cerebella identified the earliest gene expression changes in microglia cells together with endothelial cells [115], further supporting an important role of microglia dysfunction and neuroinflammation in the pathogenesis of NPC disease. Pathway analysis of differentially expressed genes revealed that activated microglia in NPC1 mice resemble those from AD mouse model, rather than those from an ALS mouse [115].
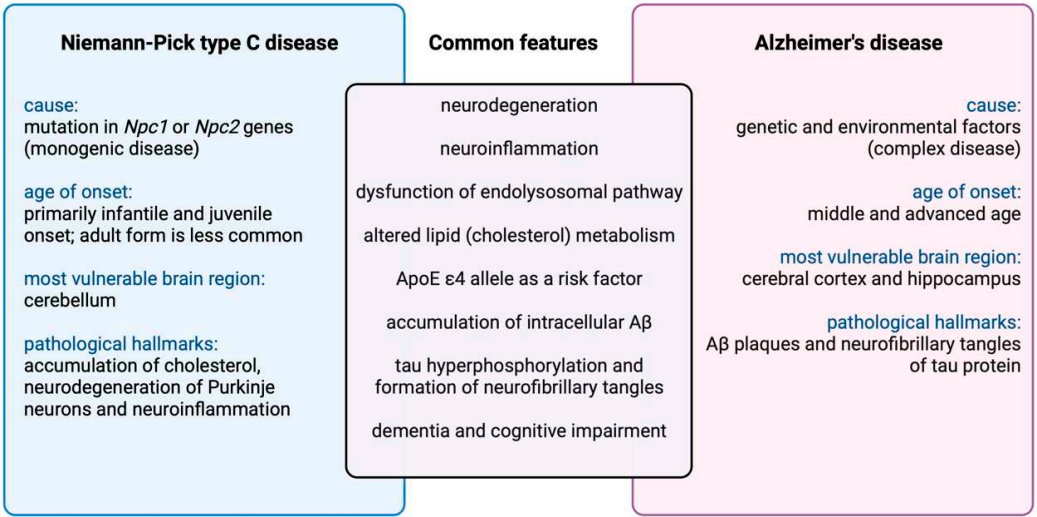
Figure 1. Common features and differences between Alzheimer's disease and Niemann-Pick type C disease. An especially prominent overlap has been observed between AD and NPC, two disorders with very distinct aetiology. Created by BioRender.com.

2.2.3. Immune imbalance in Parkinson's disease

While specific neuronal populations (dopamine neurons in the substantia nigra) are affected in PD, there is also a considerable overlap to AD and ALS in pathogenic mechanisms [24–27]. In keeping with this, complex interactions have been revealed between α-syn, a neuronal protein associated with PD and other synucleinopathies, and microglia [116]. Like in ALS and AD, microglia are neuroprotective in the early stages of disease by clearing α-syn, whereas during the chronic disease stage they are considered to promote neurodegeneration by propagating the α-syn burden and creating an inflammatory environment [117]. In addition, viral infections, including COVID-19, have been associated with an increased risk of PD [118] suggesting that inflammation linked to infection could contribute not only to AD but also to PD pathogenesis (as detailed above). Importantly, these findings suggest that neuroinflammation may be a primary pathogenic event and that systemic neuroinflammatory insults may drive transsynaptic spread of PD pathology. The link with PD, microbiota and immunity is an important topic. Retrograde axonal transport of pathology across the vagal nerve has been hypothesised in 2003 by Heiko Braak, using the model of PD [118]. The idea was that α-syn accumulation actually begins in the gut, with pathologic forms of the protein migrating into the brain through the vagal nerve. Evidence of this has been shown in 2014, with microtubule-associated transport being a key mechanism [119]. More recently, the same enteric propagation was proposed for β-amyloid in AD. In a mouse model, it has been shown that intra-gastrointestinal application of Aβ plaques leads to a higher deposition of these plaques in various regions of the brain, with retrograde vagal transport being a key pathway behind it [119]. Microbiota metabolites have also been shown to have an effect on the CNS, with short-chain fatty acids (SCFA) being the most prominent products, affecting the regulation of enteric secretion and motility as well as gut-brain signalization [120]. In various models it has been shown that SCFA can have a neuroprotective role, such as in the case of *Lactobacillus plantarum* and its product butyrate, which has anti-inflammatory effects [120]. It also positively influences blood-brain-barrier (BBB) permeability [121]. On the other hand, in some cases SCFA can have a detrimental effect, such as in the case of propionic acid, where serum levels positively correlated with motor and non-motor symptom severity in PD[121]. Besides SCFA, microbiota has also been implicated in taurine metabolism [122] as well as magnetite and hydrogen sulphite production [122], both of which have been shown to have a role in PD. Serotonin is thought to be an important part of GBA signalling, with certain bacteria affecting both its colonic and serum levels, aiding in SCFA production, which in turn increases serotonin production [123]. Microbiota also have an effect on the serotonin precursor tryptophan. It

has been shown in one study that a sex-dependent increase in hippocampal serotonin levels could be attributed to microbiota-related changes in tryptophan levels [124]. Furthermore, kynurenine, a metabolic product of tryptophan, has been shown to traverse the BBB and lead to neuroinflammation, as well as neurodegeneration [74]. Immune signalling linked to microbiota can play an important part in the development of neurodegenerative diseases [77,125]. Alterations of gut microbiota can lead to changes in the permeability of the intestinal mucus layer, leading to local immune activation and intestinal barrier dysfunction, eventually allowing various microbial triggers, such as lipopolysaccharide (endotoxin) and peptidoglycans to be released into the systemic circulation. This leads to a process known as metabolic endotoxemia, and it has been shown to trigger immune activation in various systems, including the central nervous system, most notably through microglia [126]. Macrophages have also been shown to be intrinsically linked to the gut microbiome. Antibiotics-induced changes in the microbiota have been shown to decrease macrophage levels and affect gastrointestinal motility [126]. With macrophages being essential responders to intestinal injury, this decrease could further enhance the neuroinflammatory effects of metabolic endotoxemia.

There are also direct examples of toxic insults that may influence both PD and ALS. For example, environmental exposures have been extensively studied as risk factors for PD [127]. The organophosphate pesticide, chlorpyrifos has been identified as a possible risk factor for PD in both human and animal studies, where in addition to inhibiting acetylcholinesterase, it also likely affects dopaminergic neurotransmission and produces oxidative stress [128–134]. While the role of environmental exposures in ALS is far less understood than in PD, pesticides have also been explored as risk factors, with some studies suggesting increased ALS risk with pesticide exposure, especially related to organophosphate pesticides such as chlorpyrifos [135]. Interestingly, mutations in genes specifically responsible for chlorpyrifos detoxification also seem to increase ALS risk, suggesting a gene-environment interaction in the aetiology [136,137]. With respect to genetic overlap, an example is optineurin, which has been extensively studied in ALS and glaucoma [138]; mutations may also be a risk factor in PD [139,140]. While optineurin has many roles (i.e., innate immunity, mitophagy), *in vivo* experimental PD models, alterations in mitophagy expression and localization suggest that these are likely important in both ALS and PD [141]. Taken together, there is therefore a clear pathogenic overlap between ALS and PD. Overall, there is mounting evidence that the immune system may be a primary target of PD-relevant exposure, versus just a downstream pathogenic pathway. For example, a recent line of research has advanced understating of how environmental agents interact with specific innate immune signaling pathways in microglia to stimulate conversion to a neurotoxic phenotype. Here, researchers showed that nuclear factor kappa B (NF-κB) signaling in microglia is critical to clearance of aberrant α-syn resulting from rotenone exposure, an important finding that identifies neurotoxin-immune system-phenotypic links [141].

3. Common therapeutic approaches in treating the immune (dys)functions in neurodegenerative diseases

The current treatments for NDDs are symptomatic and cannot affect and modify the underlying disease cause. However, recent understanding of multiple shared pathologies among NDDs, with considerable mechanistic overlap, has expanded to development of therapeutic targets. In fact, several emerging findings hold on the promising role of therapies able to act on the immune dysfunctions for slowing down the neurodegenerative process. As described above, many reports support the idea that molecules affecting the immune system pathways can have as a primary target the misfolded and aggregated proteins that accumulate in NDDs. The most investigated treatments include active and passive vaccinations, the molecules directly targeting the inflammatory mediators or pathways and the multimodal effects of stem cells, particularly of the mesenchymal ones (summarized in Figure 2).
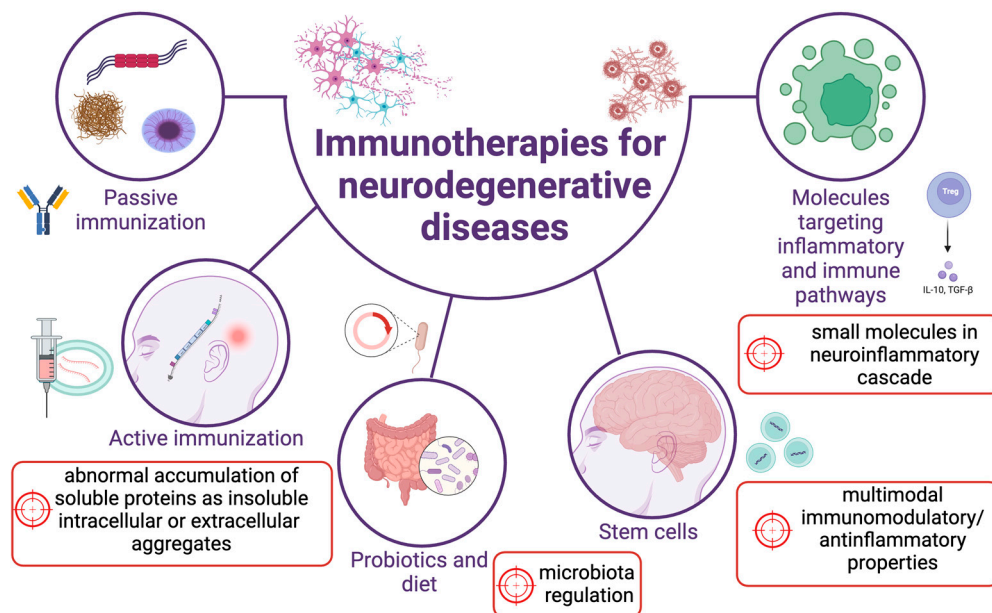
Figure 2. Schematic representation of the main immunomodulatory mechanisms currently on study as a treatment for neurodegenerative diseases.

3.1. Passive and active vaccination therapies targeting protein aggregates

In the last three decades, active vaccinations and monoclonal antibodies for passive vaccinations have been applied in several fields of medicine, including neoplastic and autoimmune diseases. More recently, this therapeutic strategy is also being evaluated for neurological diseases. In most NDDs, the primary underlying pathological mechanism is the abnormal accumulation of soluble proteins in the form of insoluble intracellular or extracellular aggregates, which can act directly as toxic aggregates or via precursors or mediators, and on which vaccination therapies can work [142]. More specifically, immunotherapeutic approaches include both passive and active immunization. The first one consists of an infusion with the monoclonal antibodies directed against the target molecules (e.g., the misfolded proteins); the second one provides specific antigens directed to a specific adaptive immune response [143], inducing the production of antibodies or modulating the inflammatory response. Certainly, the most relevant example is the removal of Aβ accumulation in AD. However, since the intracellular protein accumulation is a hallmark of most NDDs, the same approach was also used for intracellular proteins, α-syn and tau among them. We will summarize here the main clinical trials recently developed.

3.1.1. Clinical trials on Aβ immunization

Currently, passive immunization with the antibodies against Aβ is the most advanced immunotherapy under investigation. It started from solid preclinical data showing the ability of Aβ-targeting monoclonal antibodies to bind the Aβ-42 species, reducing the toxicity, preventing cell death, and restoring the plasticity at the hippocampal level in animal models [144–146]. Different Aβ-targeting monoclonal antibodies have been proposed in recent years for AD treatment. Due to different binding properties among them, we have aducanumab [147] and lecanemab [148]among the most promising. The aducanumab was approved after two large trials (EMERGE, 1638 patients and ENGAGE, 1647) with AD patients in the early stage of the disease [147]. The primary outcome was the changes over treatment in the global cognition (measured with the Clinical Dementia Rating Sum of Boxes test) (CDR-SB) [149], and it was met in the EMERGE trial but not in the ENGAGE. However, in both studies, promising results were obtained regarding biomarkers, confirming a dose-dependent reduction in AD markers pathophysiology. Based on these results, aducanumab (marketed as Aduhelm) was approved by the U.S. Food and Drug Administration in 2021 under the

accelerated approval pathway. On the contrary, the European Medicines Agency withdrew its marketing authorization application for aducanumab to treat the early stages of AD. Also for the US patients, in July 2023, lecanemab, a humanized IgG1 monoclonal antibody that binds with high affinity to Aβ soluble protofibrils, was approved (marketed as Leqembi). In the phase III clinical trial, the drug obtained its primary outcome (the same as the aducanumab trial) and reported a significant reduction in brain amyloid burden. Clinical trials on active immunization for Aβ started in 2000 [150]. The first vaccine tested in humans, called AN1792 (Elan Pharmaceuticals), provided the inoculations of amyloid-β42 peptide with an adjuvant. Albeit positive effects were observed in post-mortem neuropathological studies[151], the vaccine had several severe side effects (i.e., meningoencephalitis) and the trial was stopped. Even if without clinical efficacy, in a long-term follow-up of survived patients (14 years) [152] all had only very sparse or undetectable plaques in all regions examined. Subsequent trials in this regard obtained better safety results, but no clinical and biological effects [153].

3.1.2. Clinical trials on tau immunization

Since intraneuronal aggregates of tau protein have been shown to directly correlate with cognitive decline in AD [154,155], they comprise a potentially even more interesting target than Aβ. In the last decades, several encouraging results were obtained from the experimental mouse models, where tau targeting resulted in a reduction in protein pathology, preservation of brain volume, and improvement of behavioural scores [156]. Among the most relevant of anti-tau vaccines is AADvac1, an active peptide vaccine targeting nonphosphorylated tau, which proved safe and immunogenic in AD patients [157], although there were no clinical effects in the whole cohort. Regarding passive immunization, three studies have been completed, but the results are still unpublished (BIIB092/Gosuranemab, a humanized monoclonal antibody that binds to N-terminal tau (NCT03352557), RO7105705/ Semorinemab, an anti-tau IgG4 antibody (NCT02820896), and LY3303560/Zagotenemab, a humanized anti-tau antibody derived from MCI-1 (NCT02754830). A trial with the JNJ-63733657, a humanized monoclonal anti-tau antibody that binds to phosphorylated tau (NCT04619420), is in a recruiting phase.

3.1.3. Clinical trials on α-syn immunization

Similar as for Aβ, passive immunization for synucleinopathies involves using different monoclonal antibodies against α-syn. In a mouse model of PD, Abs-α-syn significantly attenuated the cognitive and motor deficits, with a consequent reduction of α-syn aggregates and of pathological accumulations of the levels of soluble α-syn, total human α-syn, and α-syn oligomers [158]. Starting from results in animal models, large clinical trials started. However, unfortunately, no positive results were obtained from one large trial with prasinezumab [159], observing no meaningful effect in global and imaging measures of PD progression and a large percentage of infusion reactions (up to 34% of patients). A better safety profile has been obtained in the phase I trial with BIIB054 (cinpanemab) [160], but still without effects on clinical outcomes in the first year of the trial, leading to its discontinuation and premature termination (data not published). Clinical trials on α-syn active immunization were a continuation of several studies of animal models, which showed that antibodies to α-syn prevented pathogenic protein spread and promoted clearance of aggregates [161]. Several in-human studies have been proposed. One of the most promising involved the use of PD01A (AFFITOPE). The molecule is an eight amino acid peptide that mimics an epitope in the C-terminal region of human α-syn designed to stimulate B cell antibody responses bypassing the auto-reactive T cell mobilization. The first-in-human, randomized, phase 1 study of immunizations with PD01A [162], demonstrated that the repeated administrations of PD01A were safe and relatively well tolerated in a cohort of PD patients. From a biological point of view, a substantial humoral immune response was observed. However, to date, no other results have been published.

3.1.4. Immunization for ALS treatment

For ALS, monoclonal antibodies against intracellular proteins such as SOD1, C9orf72 and TDP-43 are under study or recently completed, although several improvements are needed to increase the efficiency in ALS patients and to obtain significant results [163]. Other antibody-based interventions investigated in ALS patients targeted other molecules involved in the neuroinflammatory pathways mainly localized at intracellular and extracellular level, including the neurite outgrowth inhibitor A (ozanezumab), the muscle specific kinase, the IL-6 receptor (tocilizumab) and other proteins (namely NRP-1, myostatin, CD40L, DR-6, IFN-γ, GD1a, CTGF and HMGB1). Also in this case, the results are only preliminary, contrasting[164,165], and mainly related to biological outcomes [164].

3.2. Targeting inflammatory mediators

Although there are interesting data on the crosstalk of aggregated proteins in different models of NDDs, to date, immunotherapies targeting aggregates alone have had a limited success. This leads us to assume that a more complex scenario exists where the pathological proteins are only one facet of a much more complex therapeutic challenge. As already described, one of the most common and relevant targets of neurodegeneration in NDDs is the alteration of CNS homeostasis mediated by the immune system, where microglia and astrocytes play a central role. In the past years, several clinical trials using anti-inflammatory drugs (e.g., aspirin, prednisone, naproxen, diclofenac, indomethacin) started in patients with NDDs, including AD, PD and ALS, but all failed to obtain clinical improvements [166,167]. This suggested that a complexity between microglia, astrocytes and neurodegeneration necessitates more precise targeting, and perhaps acting further upstream in the neuroinflammatory cascade, such as on inflammatory mediators (cytokines, chemokines and growth factors) or phagocytic functions. However, converging targets with great cytolytic potential such as the complement cascade, have also been targeted. For example, some potential targets are: 1) TNF-α; the use TNF-α inhibitors (antibodies and related fusion proteins) was promising in rodent models of AD; however, two previous studies in AD obtained contrasting results, mainly related to the difficulty of the drug (etanercept) to penetrate the CNS after perispinal injection [168]. Other routes of administration have been tried (e.g. subcutaneous), but with no relevant clinical results, probably related to its inability to penetrate the BBB [168]; 2) the interleukins: evidence reported that numerous interleukins (including IL-2, IL-17, IL-22) are associated with NDDs development and progression by activating glial cells and creating a pro-inflammatory environment. Preliminary evidence for using IL-2 in AD started from solid preclinical data [169], and some trials are currently ongoing (NCT05821153 and NCT05468073); 3) the GM-CSF; GM-CSF is an immunomodulatory growth factor that is clearly deregulated in NDDs. GM-CSF has shown a strong positive effect in mouse models showing a pleiotropic neuroprotective effect with the attenuation of neuroinflammation and cognitive decline by enhancing Aβ clearance by recruiting microglia to amyloid plaques [170]. The in-human results are also encouraging: a clinical trial published in 2021 on AD patients showed that the GM-CSF (sargramostim) treatment had no adverse events in patients, changed innate immune system markers, and significantly improved cognitive status [171] A larger trial is ongoing (NCT04902703). The same drug also showed encouraging effects in PD, even in a small pilot phase I clinical trial [172]: sargramostim showed, clinically, a modest improvement after treatment compared with placebo, and biologically, a Treg number increase.

Regarding ALS, some anti-inflammatory therapies targeting the immune system yield promising results. Very recently, the group of Professor Mandrioli published interesting results on rapamycin treatment in ALS patients [173]. Specifically, the trial observed a significant decrease in the mRNA relative expression of IL-18, plasmatic IL-18 protein, and increased monocytes and memory-switched B cells. Other promising results derived by an autologous infusion of expanded Tregs plus subcutaneous IL-2: Treg/IL-2 treatments promoted, from a biological point of view, a higher Treg suppressive function and, from a clinical point of view, a slowing in disease progression [174]. Lastly, the clinical trial with masitinib is underway (NCT03127267). Masitinib is a selective, oral tyrosine kinase inhibitor with neuroprotective effect preclinically demonstrated and with promising

clinical effects in the ALS early trial stage. Interestingly, the same drug is in study also in mild to moderate AD patients (NCT05564169).

3.3. Targeting complement

As shown, the complement has a pathogenic relevance in NDDs, where the role of innate immune-driven inflammation is rapidly growing. Drug molecules that target players of the complement activation cascade can potentially stop the complement-mediated tissue damage, and some trials are ongoing in this regard in NDDs [175]. For example, in AD mouse models, positive results in terms of safety are obtained with ANX005 (a humanized immunoglobulin G4 recombinant antibody against C1q). No studies in humans are currently ongoing [176]. In ALS, similar results in mouse models were obtained using the PMX205, which could delay the grip decline and slow the disease progression [177]. Also, in ALS patients, two studies are ongoing targeting complement: the first one, a phase 2 trial with ANX005 (NCT04569435), and another phase 2 trial with Pegcetacoplan (APL-2, a complement C3 inhibitor) is ongoing (NCT04579666). Lastly, a phase 3 trial is recently terminated with Ravulizumab (a long-acting inhibitor of terminal complement protein C5) but without a positive outcome (the internal displacement monitoring Centre discontinued the study due to lack of efficacy). No trials in PD are ongoing.

3.4. Stem cell and related treatments

Due to their immunomodulatory, anti-inflammatory, and regenerative properties, stem cells and particularly mesenchymal stromal cell (MSC) treatments can have long-term effects on patients with NDDs, as recently demonstrated in ALS [178,179]. From a scientific point of view, this positive result lays the foundations for continuing research in this field, also applying it to other NDDs. MSC (Lomecel-B) have recently been preliminary tested in AD in a phase I clinical trial [180] with positive results, including improvement in cognitive function, hippocampal tropism and fluid biomarkers, providing mandatory information for larger phase II/III clinical trials. However, to date, there is no data about MSC transplantation in PD but from one preliminary report autologous bone marrow-MSCs injected into the subventricular zone appeared safe and well-tolerated, also with minimal motor function improvement [181,182].

Another important avenue in the treatment of NDDs are represented by exosomes. MSCs - derived exosomes demonstrated to exert more potent therapeutic effects over MSCs in NDDs, principally by delivering anti-neuroinflammatory processes [181,182]. Currently some clinical trials to test efficacy of exosomes in AD (NCT0438 8982) and PD (NCY01860118) are ongoing.

3.5. Targeting microbiota

With lot of the pathways behind gut-brain signalling still waiting to be discovered, the main incentive for further research should be potential therapeutic methods targeting the gut microbiota. Antibiotics have shown a positive effect on PD pathology in mice, either by altering microbiota composition [183] or inhibiting α-syn fibrillation [184]. Similarly, probiotics have been shown to prevent neuroinflammation and cognitive dysfunction also by modifying microbiome composition [185]. Specific diets are known to have a beneficial effect in neurodegenerative diseases such as AD and PD, most notably the Mediterranean diet, which is rich in *Lactobacilli* [186]. Certain clinical studies have shown promise, such as in the case of enema application [187,188] or fecal microbiota transplantation [189] In conclusion, since a great body of knowledge shows microbiome changes in NDDs, the gut, as an often-neglected organ in treating NDDs, should be taken into account. In time, microbiota regulation could prove to be a powerful tool for the prevention and management of neurodegenerative disorders.

3.6. Potential future therapies

Preventive vaccination and/or boosting for influenza virus, HSV-1, and herpes zoster virus have already been conclusively linked to decreased risk for dementia [190,191]. Similar effects were

reported for vaccines to prevent pneumococcal pneumonias. Although these vaccinations are still not a standard of care for adult populations in most countries, it is advisable that these notions are considered in future preventive measures for NDDs.

Regarding PD, the primary limitation from advancing beyond dopamine replacement therapies has been that most patients are diagnosed well after significant neuropathology has occurred. As earlier biomarkers are developed, the likelihood of successful bench to bedside translation for novel interventions would be expected to increase. As one promising example, a recent study found that mtDNA damage was increased in peripheral blood mononuclear cells derived from patients with idiopathic PD and those with the PD-associated leucine-rich repeat kinase 2 (LRRK2) G2019S mutation in comparison with age-matched controls. Importantly, mtDNA damage was elevated in non-disease-manifesting LRRK2 mutation carriers, suggesting that those with known risk factors, but not yet with a PD phenotype (not all will convert) could be identified prior to diagnosis. Of note, LRRK2 has a critical role in the central and systemic immune systems. These findings point to a broad future approach, where PD patients are identified earlier or may even be treated at prodromal stages with specific immune modulators.

Current treatments of NPC aim to lower the accumulation of free cholesterol and other GSLs in late endosomes/lysosomes – the primary feature of NPC disease. However, the use of miglustat or methyl-β-cyclodextrin, which inhibit cholesterol synthesis or reduce its accumulation, respectively, can only alleviate symptoms somewhat, but cannot sustainably halt the progression of the disease [192–196]. Given the overlap between AD and NPC pathology, including Aß plaque formation, tau accumulation, and early neuroinflammation (activation of microglia), future therapeutic options against NPC may benefit from those already tested in AD.

4. Conclusions

With their complex genetic and environmental aetiology and an ever-increasing incidence in modern societies, NDDs remain one of the leading medical challenges. Given an extensive overlap in many adult-onset neurodegenerative diseases, particularly AD, PD, ALS and FTD, it is encouraging that many of the potential immunosuppressive and immunomodulatory treatments directly targeting immune mediators have been studied across different NDDs. A prerequisite for moving forward were two paradigm shifts regarding immunity in NDDs, that is that immune mechanisms are not merely noxious but also protective, and that inflammation likely plays a role as a trigger not only a distal element but can contribute to early pathogenesis of the disease. The first resulted in a deeper understanding of mechanisms and designing more nuanced targeted therapies instead of using broadly acting immunosuppressants, whereas the second will in time perhaps allow us to focus more on prevention and vaccinations to mitigate the risk for NDDs. Common targets for immunomodulatory treatment are of specific interest, and it is encouraging that some have also shown promising results across the NDD spectrum (Tregs, complement, etc). In conclusion, given the multifactorial nature, the numerous disease mechanisms, and the overlapping proteinopathies in the different NDDs, combining treatments acting on different disease pathways may allow an integrated and synergic disease-management intervention, personalized on a single patient.

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