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Review

Hallmarks of neurodegenerative diseases

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https://doi.org/10.1016/j.cell.2022.12.032

SUMMARY

Decades of research have identified genetic factors and biochemical pathways involved in neurodegenerative diseases (NDDs). We present evidence for the following eight hallmarks of NDD: pathological protein aggregation, synaptic and neuronal network dysfunction, aberrant proteostasis, cytoskeletal abnormalities, altered energy homeostasis, DNA and RNA defects, inflammation, and neuronal cell death. We describe the hallmarks, their biomarkers, and their interactions as a framework to study NDDs using a holistic approach. The framework can serve as a basis for defining pathogenic mechanisms, categorizing different NDDs based on their primary hallmarks, stratifying patients within a specific NDD, and designing multi-targeted, personalized therapies to effectively halt NDDs.

INTRODUCTION

Neurodegenerative diseases (NDDs) are a heterogeneous group of neurological disorders adversely affecting the lives of millions of people worldwide and entail the progressive loss of neurons in the central nervous system (CNS) or peripheral nervous system (PNS). The collapse of the structure and function of neural networks and loss of neurons, which are unable to efficiently renew themselves due to their terminally differentiated nature, result in the breakdown of the core communicative circuitry, culminating in impaired memory, cognition, behavior, sensory, and/or motoric function.

In this review, we argue that a set of hallmarks define NDDs, namely: pathological protein aggregation, synaptic and neuronal network dysfunction, aberrant proteostasis, cytoskeletal abnormalities, altered energy metabolism, DNA and RNA defects, inflammation, and neuronal cell death (Figure 1).

We describe these hallmarks and their evidence in the context of prevalent NDDs,[1–3] including Alzheimer disease (AD),[4–9] Parkinson disease (PD),[10–12] primary tauopathies,[13,14] frontotemporal dementia (FTD),[15–17] amyotrophic lateral sclerosis (ALS),[18–20] synucleinopathies[12,21–23] (i.e., Lewy body dementia [LBD] and multisystem atrophy [MSA]), Huntington disease (HD)[24,25] and related polyglutamine (polyQ) diseases[26–28] (including spinocerebellar ataxias [SCA]), prion disease (PrD),[29–31] traumatic brain injury (TBI),[32,33] chronic traumatic encephalopathy (CTE),[32,33] stroke,[34,35] spinal cord injury (SCI),[36] and multiple sclerosis (MS).[37,38] The epidemiology, symptoms, genetics, and pathological signatures of these specific NDDs have been elegantly and extensively reviewed previously[1–4,10–42] (Figure 2). In this work, we define an NDD hallmark as a cellular or molecular process that fulfills the following criteria: (1) is linked to (rare) genetic forms of NDDs, (2) contributes to sporadic forms of NDDs, (3) contributes to neurodegeneration and neuronal loss in preclinical models and NDD patients, and (4) molecular markers that are reflective of the hallmark are altered.

In addition to describing the hallmarks and the genetic and biological evidence for these hallmarks, we highlight the interrelationships of the underlying cellular and molecular processes and how hallmarks can be detected and monitored using biomarkers *in vivo*. We propose that the neurodegenerative process in NDDs is driven by combined defects in multiple NDD hallmarks, pointing to the need for multi-targeted therapies. The primary or main NDD hallmarks driving a specific NDD in an

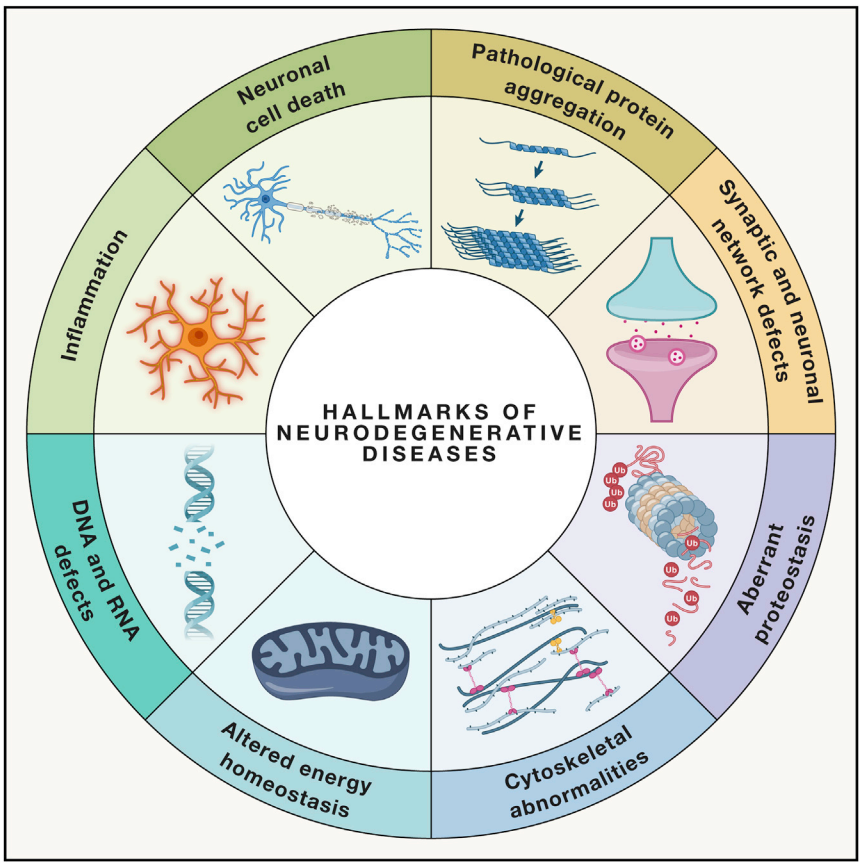


Figure 1. Hallmarks of neurodegenerative diseases

The scheme identifies and illustrates the eight hallmarks described within the article. Based on decades of basic, translational, and clinical research, genetic factors and biochemical pathways underlying many NDDs have been identified, resulting in the identification of eight NDDs hallmarks: pathological protein aggregation, synaptic and neuronal network dysfunction, aberrant proteostasis, cytoskeletal abnormalities, altered energy homeostasis, DNA and RNA defects, inflammation, and neuronal cell death.

individual will depend on the NDD insult and on the neuronal vulnerability and resilience, i.e., the ability to handle and protect against insults, of the individual and the affected brain region.

We here present a framework to study NDDs using a holistic approach that involves the interconnectedness and combined involvement of multiple hallmarks in the neurodegenerative process. This overarching framework can be used for understanding the molecular mechanisms of neurodegeneration, for categorizing different NDDs based on the primary hallmarks, for stratifying subtypes and patients within specific NDDs based on the primary hallmarks, and for designing combinatorial or personalized therapeutic strategies to effectively halt NDDs.

PATHOLOGICAL PROTEIN AGGREGATION

Pathological protein aggregates are hallmarks of NDDs

Characteristic protein aggregation is a key pathological hallmark of a variety of NDDs and often serves for diagnosis and disease classification (Figures 1 and 3).[1,2,29,39,43] These NDDs classify as proteinopathies and include: AD, PD, primary tauopathies (including progressive supranuclear palsy [PSP], corticobasal degeneration [CBD], tau-linked frontotemporal dementia [FTD-tau]), FTD, ALS, synucleinopathies (including LBD and MSA), HD and related polyQ diseases (including SCA), and PrD.[1–30,39–43] The characteristic aggregating protein, linked genes, symptoms, and affected brain regions of these different NDDs are presented in Figure 2[1–30,39–42,44–48] and further used in this review. Notably, for many NDDs, protein aggregates are found in brain regions that correlate with clinical outcomes, supporting their pathogenic role in NDDs, whereas selective neuronal vulnerability needs to be considered (Figure 2).[2–5,8–21,24–30,39–49]

Mechanistic insights from genetics: Gain of toxic function versus loss of function

The identification of causal mutations for (rare) inherited forms of NDDs has aided the search for pathogenic mechanisms of NDDs.[3,9,19,39,43,47] A causal link between these disease-causing mutations and increased aggregation of the encoded protein is a common feature among different NDDs, supporting a toxic gain-of-function mechanism.[3,43] This link between inherited mutations and increased aggregation has been shown for several genes, including those encoding amyloid precursor protein (APP) (AD), tau (AD and tauopathies), α-synuclein (PD and synucleinopathies), PrP^{C} (PrD), SOD1 (ALS/FTD), TAR DNA-binding protein 43 (TDP-43) (ALS/FTD), FUS (ALS/FTD), and huntingtin (Htt) (HD).[3,7,12,19,23,29,43,48,50,51] The fact that mutations in different NDDs enhance aggregation of the characteristic NDD protein points to a central pathogenic role for protein aggregation in NDDs.[3,5,7,9,19,23,29,43–45,47,48,50–55] Furthermore, NDD mutations have been identified in genes such as *Presenilin 1* and *2* (*PSEN1, PSEN2)* that do not lead to aggregation of the encoded protein but instead increase aggregation of key NDD proteins.[3,7,9,45] Another gain-of-function mechanism is the generation of aggregating dipeptide repeats (DPRs) from hexanucleotide repeat sequences, generated by repeat-associated non-ATG (RAN) translation.[20,28,44,54,56,57] The close correlation between the aggregation process and symptom progression in most NDDs and the fact that aggregating proteins affect crucial neuronal functions and NDD hallmarks (outlined below) further support a toxic gain of function.[8,19,23,39,40,42,43,48,49,58] However, it is important to note

that the physiological roles and normal function of genes linked to NDDs are also connected to different hallmarks of NDDs (for example for tau,[59] APP,[60] α-synuclein,[61] SOD1,[51] FUS,[51] and TDP-43[53] [outlined below]). Furthermore, aggregation and protein sequestration in one part of the cell can lead to loss of its presence in another, and hence, the loss of its physiological function. Combined effects of toxic gain and loss of function could lead to concomitant defects in NDD hallmarks or a multi-hit process that drives neurodegeneration (Figures 1 and 3).

Prion-like propagation

In PrD, misfolding of the prion protein and rapid propagation of its aggregation has been identified as the principal mechanism responsible for spreading neurodegeneration between cells and brain regions.[29,31,42,52] The fast, dramatic loss of neurons and network function in PrD provides a convincing argument for protein aggregation and its propagation as an important driver of the neurodegenerative process and hence as an NDD hallmark (Figures 1 and 3). This mechanism provided a novel concept for both PrDs and other NDDs.[23,29–31,39,42,48,50,52,58] In the context of NDDs, the term "prion-like" differentiates these proteinopathic seeds from true prions as there is no evidence for transfer between individuals. The prion-like concept also led to the identification of different strains of prion-like seeds in NDDs,[23,39,48,58,62] which correlate with toxicity and aggregation and propagation propensity. Consequently, prion-like processes are considered contributors to neurodegeneration and the characteristic spatio-temporal progression of pathology in proteinopathic NDDs, although selective neuronal vulnerability remains to be considered[23,39,41,48,50,58] (Figures 1 and 3).

Protein aggregation and toxicity

Although protein aggregation largely correlates with symptom progression in proteinopathic NDDs, this does not directly imply that mature aggregates are the major toxic culprits. Notably, intermediate oligomeric assemblies have been proposed as neurotoxic candidates.[63] Both mature fibrillar aggregates and oligomeric assemblies are present extra- or intra-cellularly, in different cell types and in different subcellular locations depending on the protein involved (i.e., nuclear, cytoplasmic, and pre- or post-synaptic), enabling their interference with different NDD hallmarks (outlined below),[7,10,12,14,19,21,22,24,25,27,44,64–67] (Figures 1 and 3), although the exact toxic mechanism and the toxic forms of these aggregates have not yet been unequivocally defined. Of note, protein aggregates do not always correlate perfectly with the disease process. For instance, for some DPRs, the correlation with disease progression is rather weak,[68] and in some genetic cases (e.g. linked to Leucine-rich repeat kinase 2 gene [*LRRK2*] or Parkin gene [*PRKN*]) no fibrillar protein aggregates are observed.[69] These findings suggest that in these cases alternative mechanisms need to be considered for neurotoxicity and that molecular events distinct from aggregating proteins contribute to the disease.

Biomarkers for NDD protein aggregation

Several well-characterized biomarker assays for protein aggregation with diagnostic value for NDDs have been developed. For example, amyloid-positron emission tomography (PET) and the ratio of 42–40 amino acid-long Aβ (Aβ42/Aβ40) peptides in cerebrospinal fluid (CSF) can be used to monitor amyloid deposition in the context of AD. In fact, both assays detect the onset of Aβ aggregation decades before clinical disease onset.[70] Plasma Aβ42/Aβ40 can also be used to detect early Aβ pathology, although it shows lower absolute differences than CSF.[71,72] Additional markers that reflect amyloid build-up in the brain are CSF and plasma phosphorylated forms of tau, reflecting a link between both pathological processes in AD.[73] The best-established biomarker for tau pathology in AD is tau-PET.[49,74,75] Importantly, tau-PET is less suited for primary tauopathies and secondary non-AD tauopathies (e.g., CTE) than for AD tauopathy, due to conformational differences. For TDP-43, α-synuclein or prion aggregates, it has been more difficult to develop classic fluid biomarkers that are pathology-specific. However, the fact that these proteins may spread in a prion-like manner sparked the idea that seeding aggregation assays, such as real-time quaking-induced conversion (RT-QuIC) or protein-misfolding cyclic amplification (PMCA), could be used to qualitatively detect pathological forms of the proteins in CSF. Studies analyzing lumbar CSF with RT-QuIC or PMCA of prion protein and α-synuclein have been developed into clinical tests with excellent diagnostic accuracy and neuropathological confirmation.[76]

Non-proteinopathic neurodegenerative disorders

Based on the above evidence, protein aggregation is considered an important contributor to the neurodegenerative process in proteinopathic NDDs. However, the role of protein aggregation in NDDs with a primary traumatic, ischemic, or inflammatory component may be less clear. Such non-proteinopathic diseases include TBI,[32,33] CTE,[32,33] stroke,[34,35] SCI,[36] and MS,[37,38] where the primary insult is not obviously related to protein aggregation. Nevertheless, several of these NDDs display protein aggregation as a presumed secondary effect, contributing to a chronic aggravating phase (e.g., tau and TDP-43 in TBI[32] and CTE,[32] tau and neurofilament in MS,[77] and tau in SCI[78]). There are also genetic NDDs in which proteinopathy is not observed, e.g., spinal muscular atrophy (SMA), recessive parkinsonism, and some genetic PD cases (e.g. *LRRK2*). We therefore cannot always assign a primary role of protein aggregation in the pathogenesis of all NDDs, but protein aggregation can contribute to disease progression in combination with other hallmarks of NDDs.

SYNAPTIC AND NEURONAL NETWORK DYSFUNCTION

In NDDs, symptoms typically reflect the disturbance of specific neuronal networks,[79–81] and synaptic failure and toxicity seem to be an early event preceding neuronal loss in many NDDs (Figures 1 and 3).[4,22,35,46,64,67,79,82–93] Neuronal network function requires precise synaptic function, as well as controlled regulation of synapse stabilization and elimination. Synaptic function in turn is modulated by neurotransmitter[91–93] and calcium changes,[91,93,94] cytoskeletal adaptations,[95] presynaptic vesicle dynamics, and post-synaptic signaling[91–93,96] (Figure 3). Synaptic function requires a tight regulation of mitochondrial function and energy supply[97–100] to maintain calcium homeostasis and ionic balance, including by membrane pumps that reset ion gradients during neuronal signaling.[97,98] Energy is also required

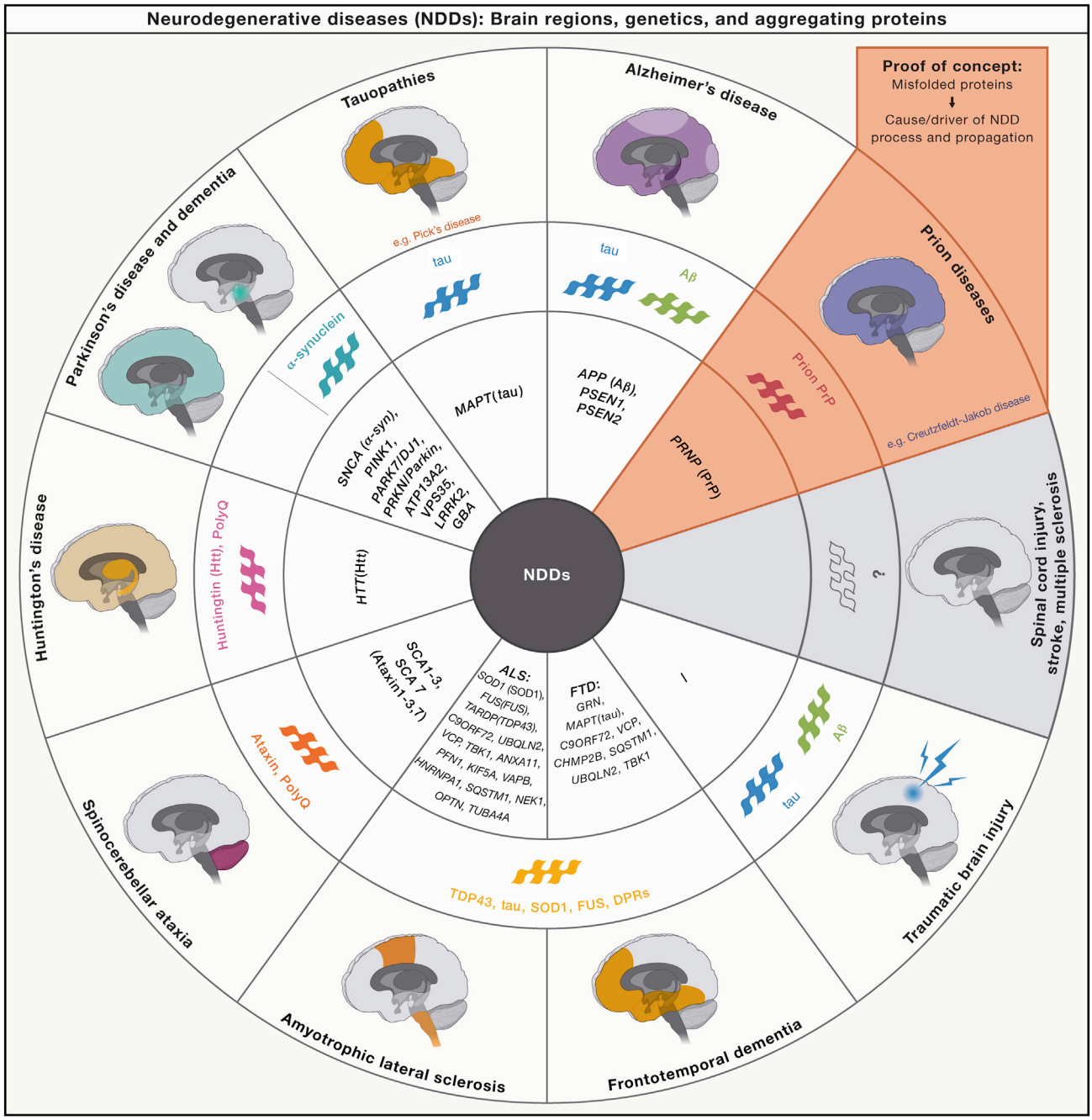


Figure 2. Characteristic aggregating proteins, genes linked to and affected brain regions in NDDs

Respective NDDs and the affected brain regions are indicated in the outer circle. Their respective symptoms, the affected brain regions, the associated genes, and aggregating proteins have been previously described in detail. Characteristic aggregating proteins in NDDs include Aß peptides formed by cleavage of amyloid precursor protein (APP) (*APP* gene), tau (*MAPT* gene), α-synuclein (*SNCA* gene), TAR DNA-binding protein 43 (TDP-43) (*TARDBP* gene), superoxide dismutase [Cu-Zn] (SOD1) (*SOD1* gene), dipeptide repeat proteins (DPRs) (*C9orf72* gene), FUS RNA-binding protein (*FUS* gene), huntingtin (PolyQ) (*HTT* gene), polyQ proteins (PolyQ), and cellular prion protein (PrP^{C}) (*PRNP* gene). A non-exhaustive list of causal and highest risk genes linked to the different NDDs is indicated in the inner circle (capital, italic).

for elimination and replenishment of constituents for proper synaptic function,[100,101] which demands tightly controlled and coordinated axonal transport, cytoskeletal dynamics, proteostasis, lipid and RNA metabolism,[97,98] autophagy,[102,103] and mitochondrial homeostasis.[99,100,104,105] Furthermore, astrocytes and microglia play important non-cell autonomous roles in energy and neurotransmitter homeostasis, synapse elimination and stabilization[106–110] (Figure 3).

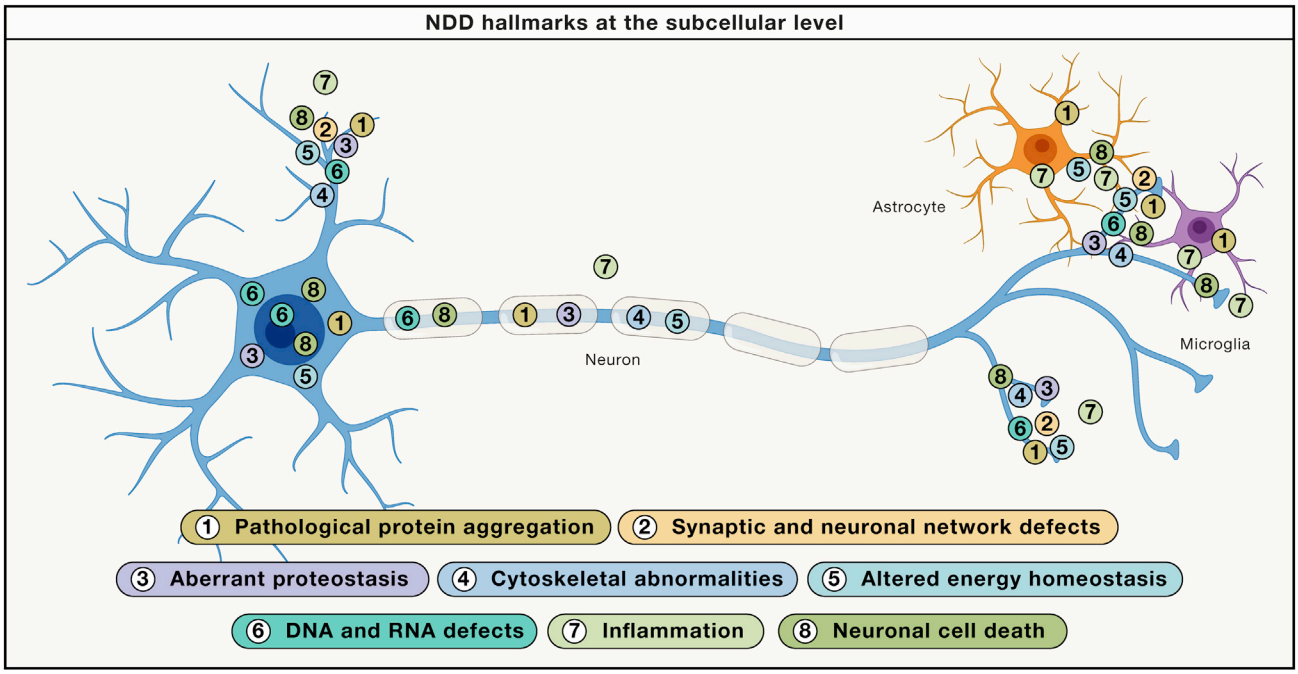


Figure 3. Schematic presentation of the NDD hallmarks and their location

A schematic presentation of the different NDD hallmarks (numbered) and their location in the modeled neuron and/or accompanying glial cells is presented for pathological protein aggregation (1), synaptic and neuronal network dysfunction (2), aberrant proteostasis (3), cytoskeletal abnormalities (4), altered energy homeostasis (5), DNA and RNA defects (6), inflammation (7), and neuronal cell death (8).

Several reviews highlight the genetic, preclinical, and patient-derived evidence that supports a key role of synaptic failure and dysfunction in NDDs.[4,18,22,35,46,52,64,66,79,82–88,107–113] For example, synaptic dysfunction (i.e., hyperexcitation or excitotoxicity) combined with calcium dyshomeostasis and energy depletion plays a key-role in stroke.[35,91–94,114–117] Excitotoxicity by excess glutamate causes neuronal death by excessive Ca^{2+} influx. Increased Ca^{2+} causes mitochondrial dysfunction and concomitant energy depletion, as well as activation of enzymes, such as calpains, resulting in degradation of proteins and lipids, dysregulation of physiological functions, and ultimately cell death.[35,91,114–116] Neuronal hyperexcitability and glutamate-mediated excitotoxicity have also been considered important mechanisms in the etiology of ALS[18,46,85,111,118] and may contribute to the neurodegenerative process in HD,[26,83] AD,[87,90] MS,[107] SCI,[36] and TBI as well.[33] Furthermore, several proteins that aggregate in NDDs exert a physiological role at the synapse and/or associated pathological forms induce synaptic failure or dysfunction,[59–61] underscoring the interconnectedness of NDD hallmarks (e.g., α-synuclein[61,112,113,119,120] in PD, Htt[25,83] in HD, APP/Aβ and tau in AD, and tauopathies[64,87]). Additionally, several genes that are linked to proper synaptic function are known to be mutated in certain NDDs (for instance *SNCA, SYNJ1, DNAJC6*, and *DNAJC13* in PD,[113] and *C9orf72*[121] in ALS/FTD). Hence, a combination of hypo- and hyper-active synapses are likely to be observed in NDDs, causing a complex pattern of deregulated neurotransmission in the brain.[87,90,99,111,118]

Synaptic failure and dysfunction in NDDs have been described as an early event before neurodegeneration in AD, PD, HD, FTD, ALS, and stroke.[64,67,79,82–88,90,111] For instance, synaptic failure and synapse loss in AD occurred before neuronal loss,[64] whereas hyperexcitability was also shown in different brain regions.[64,87,90] Similarly, synaptic and axonal decay precedes neuronal loss in PD,[113,122] and at symptom onset, synaptic dysfunction exceeds the loss of dopaminergic neurons.[113] Symptoms and synaptic defects were also found to precede overt neuronal loss in HD,[83] and the disconnection between motor neurons and muscle is observed before motor neurons die in ALS.[18] Further supporting a role for synaptic defects in NDDs, expression of pathogenic mutants, such as APP,[64] tau,[123] α-synuclein,[119] Htt,[83] and various ALS/FTD genes, induces synaptic and neuronal network dysfunction in preclinical models and is spatially and temporally associated with early protein aggregates, particularly oligomeric aggregates.[82,123] Aggregation of various NDD proteins can occur within synapses,[124] either at the pre- or post-synaptic specialization,[67,120,121] and is associated with adverse effects on synaptic function.

A role for synaptic function is further suggested by symptomatic improvement of NDDs following administration of medication based on modulation of neurotransmission. A powerful example of neurotransmission modulation is the replacement of the lost dopamine signal in PD[10,11] using the precursor L-DOPA, which is temporally effective at restoring motor symptoms in early to moderate disease.[11] A role for synaptic function is further suggested by variable, mild symptomatic improvement for several months following administration of acetylcholinesterase inhibitors and NMDAR-antagonists in AD,[1] riluzole, which modulates glutamatergic neurotransmission, in ALS,[111] and

tetrabenazine that modulates dopaminergic signaling in HD chorea.[1]

Synaptic defects can be detected by a number of imaging modalities in NDD patients. Functional magnetic resonance imaging (fMRI), which assesses neuronal network connectivity, indicates early network dysfunction in NDDs.[64,75,79,87,90,118] Fluorodeoxyglucose-PET (FDG-PET) reveals decreased glucose metabolism in AD, in line with decreased neuronal function in the disease. Additionally, a PET method that images synaptic density using a ligand targeting the synaptic vesicle protein 2A (SV2A) was recently developed,[125] and there are now also targeted assays to measure panels of pre-, trans-, and post-synaptic proteins in CSF, with promising findings across NDDs.[126]

Synaptic and neuronal network dysfunction closely interacts with other NDD hallmarks (Figure 3). As described above, correct synaptic and neuronal network function requires correct functioning of and interaction with the core physiological processes related to NDD hallmarks. As such, synaptic dysfunction and excitotoxicity are both closely linked to defective energy metabolism, oxidative stress, (local) protein production by axonal transported RNA, protein and organelle degradation, cytoskeletal dynamics, and neuronal death.[96–105] Conversely, the synapse may act as a cell-autonomous initiator of cell dysfunction and death, depending on the vulnerability and resilience of the neuron. Additionally, non-cell autonomous processes may contribute to synaptic damage.[106,107] For example, microglial activation may lead to inappropriate synaptic pruning,[108,109] can contribute to propagation of misfolded proteins at the synapse, and may affect microglial/astrocytic interactions that are key to synaptic function.[106,108,109]

ABERRANT PROTEOSTASIS

The accumulation of ubiquitinated, aggregated proteins in many NDDs (e.g., tau, TDP-43, α-synuclein, Htt,…), as well as the presence of p62 in NDD aggregates, indicates altered proteostasis in NDDs[2,43,127–132]; accumulating evidence further implicates aberrant proteostasis in NDDs[2,43,127–132] (Figures 1 and 3). The ubiquitin-proteasome system (UPS) and autophagy-lysosome pathway (ALP) constitute two major cellular mechanisms for maintaining protein homeostasis.[101–103,127,129–137] The UPS mainly degrades marked proteins,[127,130] whereas ALP clears protein aggregates and defective organelles, including the degradation of damaged mitochondria by mitophagy,[131,132] through the engulfment of cellular material by a double-membrane structure, the autophagosome.[129,131,132,136,137] The UPS and ALP involve ubiquitylation to target proteins and cargo for degradation and are linked by p62 (SQSTM1), which binds ubiquitin and targets cargo to the ALP, with fusion to autophagic vesicles and subsequent lysosomal degradation being the final step.[130–132] They are induced by starvation or stress conditions involving low energy or low availability of constituents (namely specific amino acids) and following clearance of damaged proteins and organelles in the cytosol provide new constituents for macromolecule synthesis and energy substrates,[131,132,134,138] highlighting their interconnection with other NDD hallmarks. The ALP also acts at the axon[133] and synapse,[102] where it contributes to local protein homeostasis[113] and mitophagy[131] that is required for effective synaptic function. Dysregulated autophagy and lysosomal function are tightly linked to cell death pathways, leading to neuronal death.[114,139,140]

The ubiquitin-proteasome system

An active role of the UPS in NDDs is supported by the observation that several genes linked to familial forms of NDDs maintain key functions in the UPS response.[127] Mutations in two UPS components, UBQLN2[141] and VCP,[142,143] which are central for ubiquitination and proteasome targeting, are associated with ALS/FTD. Additionally, Parkin (a PD-linked gene) encodes a ubiquitin-protein ligase, and UCHL1, linked to a rare progressive NDD form, encodes a ubiquitin carboxy-terminal hydrolase, further pointing to a role of the UPS in NDDs.[127,129,131,132,144] Moreover, aggregation of proteins associated with sporadic NDDs, such as tau, TDP-43, α-synuclein and polyQ-containing proteins, impairs UPS function, suggesting a wider association with more common forms of NDD.[127,145–148] Heat-shock proteins, including HSP70 and HSP90, which are key players in facilitating protein folding, have been shown to modulate turnover or stabilization of misfolded Aβ,[149] tau,[150] α-synuclein,[151] and TDP-43.[150,152] Finally, protein aggregation has been linked to decreased ATP levels,[153] bringing together protein aggregation and neuronal energy metabolism (discussed later), emphasizing potential exacerbating interactions between the different NDD hallmarks.

The autophagy lysosomal pathway

Consistent with autophagy being critical for neuronal health, deficiency of some atg genes, known to be critical for autophagy regulation,[129] causes neurodegeneration. As such brain-specific inactivation of autophagy by knockout of Atg7 in mice causes neurodegeneration and premature death with concomitant accumulation of aggregated proteins.[128] Similarly, postnatal neuronal deficiency of Atg5 results in neurodegeneration and accumulation of aggregated proteins in mice.[154] Chaperone mediated autophagy also prevents collapse of the neuronal metastable proteome that includes AD-related proteins.[155] Moreover, several genes linked to NDDs exert physiological roles in the regulation of autophagy.[129,131,132] Mutations in the *SQSTM1* gene encoding the p62 protein, which links UPS and ALP by binding ubiquitin and targeting cargo to the ALP, give rise to ALS/FTD cases.[130,156] Genes associated with PD exert crucial roles in autophagy, lysosomal function, and endolysosomal trafficking,[19,112,113,157] including several key proteins (i.e., *LRRK2*, *SYNJ1*, *DNAJC6*, and *DNAJC13* [RME-8]) important for controlling endocytosis and autophagy at the synapse.[102,113] Similarly, genes associated with NDDs encode proteins (i.e., PINK1, Parkin, LRRK2, α-synuclein, Htt, and ataxin 3) that are involved in autophagy, endolysosomal trafficking, and protein degradation.[113,129,131,132,135,157] The ALP also acts at the level of the synapse, contributing to synaptic protein homeostasis[103,113] and consequently accurate synaptic function. Furthermore, aggregating proteins have been detected at pre-and post-synaptic sites where they can cause dysregulation of the ALP and synaptic function.[67]

Evidence for a role of lysosomal dysfunction in neurodegeneration is furthermore emphasized in lysosomal storage disorders (LSDs).[129,132] A large family of LSDs exists where

neurodegeneration is part of the clinical disease presentation due to recessive loss-of-function mutations. These early onset neuropathic forms of disease include among others Niemann-Pick's disease type C1 (NPC) and Gaucher disease, which are linked to lysosomal defects that give rise to altered cholesterol or lipid homeostasis, respectively.[129,131] Interestingly, there is a striking parallel in some of the symptoms and aggregating proteins of LSDs with certain NDDs (e.g., tau in NPC).[132] Conversely, some genes associated with NDDs are linked to LSDs, such as GBA (β-glucocerebrosidase) and GRN (progranulin),[129,131,132,135,158] and some genes associated with NDDs exert key lysosomal functions (for example ATP13A2 [lysosomal polyamine exporter] in PD).[131,132,144,157,159–162]

Aggregating proteins adversely affect ALP function, and the ALP also appears to play a role in the cell-to-cell transfer of aggregation-prone proteins, similar to the prion-like propagation discussed earlier. For example, endolysosomal trafficking following uptake of tau-seeds and subsequent lysosomal rupture promotes cytosolic access to aggregated tau.[163] Additionally, α-synuclein-seeds taken into cells have disruptive effects on lysosomal function.[164] Biomarker panels for lysosomal proteins have been developed and altered concentrations have been observed in both PD and AD,[165] but more studies are needed for their detailed understanding and further use.

Lysosomal and autophagic dysfunction connect to neuronal cell death, explaining the associated neurodegeneration in LSD.[114,140] Furthermore, ALP is induced in conditions of starvation, i.e., during low energy or nutrient availability to replenish nutrients. ALP is essential for mitophagy and hence proper mitochondrial function,[131] further highlighting a tight link between ALP and energy resources. Moreover, failing proteostasis and protein aggregation causes the sequestration of proteins, thereby preventing their physiological activities in processes such as cytoskeletal dynamics, synaptic function, and energy homeostasis. In addition, ALP is tightly linked to synaptic[102,113] and axonal (dys)function.[133] Thus, collectively, disrupted proteostasis can negatively interact with multiple NDD hallmarks, painting a picture of how several hallmarks can function together to induce neurodegeneration[158] (Figure 3).

CYTOSKELETAL ABNORMALITIES

The neuronal cytoskeleton consists of three main polymeric structures that interact with each other, distinguished by their protein composition and diameter[166]: (1) tubulin-based microtubules,[105,167] (2) intermediate filaments (neurofilaments),[168] and (3) actin-based microfilaments.[95] These structures allow neurons to build, maintain, and transform their architecture as well as to facilitate the organization and transport of intracellular cargoes and mitochondria along their extended lengths, thereby supporting energy homeostasis and synaptic function. Pre- and postsynaptic structures have a specialized and dynamic cytoskeleton to support their dynamic function, structure, and high energy demands, serving as anchor sites for mitochondria (microtubules) and as drivers of plastic changes (actin).[95,97–99] Axonal transport regulates the transport of proteins, lipids, mRNA, and organelles including mitochondria to synapses, thereby exerting a crucial role in neurotransmission, trophic signaling, and stress responses.[169–171] NDDs are associated with neuronal cytoskeletal alterations leading to the loss of the ability to transmit information and cargo, including mitochondria for meeting energy demands and essential core components between the cell body and the synaptic endings, often resulting in a dying-back (or a dying-forward) process[95,97–100,104,105,133,169–172] (Figures 1 and 3).

The discovery of mutations in the neuronal intermediate light filament (*NEFL*) gene in Charcot-Marie-Tooth disease (CMT)[173] and *MAPT*[13] encoding the microtubule binding protein tau in tauopathies (e.g., FTD-tau, CBD, and PSP[13]) is direct evidence for the importance of altered cytoskeletal function in NDDs. Moreover, many NDDs contain aggregates of neuronal cytoskeletal proteins, i.e., tau, actin, or neurofilament.[8,13,32,77,168,174,175] Defects in axonal transport and cytoskeletal dynamics have been implicated in a variety of NDDs including AD, PD, FTD, HD, ALS, and SMA among others.[99,100,169,170,176–178] For several components of the axonal transport machinery, including kinesin (KIF5A) and dynactin, gene mutations have been identified that are linked to NDDs (Charcot Marie tooth [CMT]/ALS/spastic paraplegia [SPG]).[176,179,180] Moreover, the neurodegenerative phenotype in several mouse models has been linked to spontaneous mutations in components of the cytoskeleton machinery.[178] These data indicate that defects in the neuronal cytoskeleton and associated functions, such as axonal transport, play a central role in NDD. A role for axonal injury in NDDs is also reflected in the extensive neurodegeneration in NDDs, where distal axons are severed from the cell body, resulting in build-up of materials at the end of the axonal stump and breakdown of the axonal cytoskeleton.[171] In SCI, axonal injury is also associated with ischemia, energy depletion, excitotoxicity, and inflammation, further driving the neurodegenerative process.[36,171,172] In the chronic phase of SCI, axonal dying-back and Wallerian degeneration occur, highlighting the importance of the cytoskeletal structure in maintaining neuronal cell function and survival.[170–172]

Axonal dysfunction and degeneration are recognized as prominent contributors to disease progression in ALS, MS, TBI, and PD, as well as in PNS and ocular disorders.[18,33,65,99,100,169–172,176,181] In ALS, spinal-bulbar muscular atrophy (SBMA), spinocerebellar disorders, and peripheral neuropathies, destruction of distal regions of long axons precedes overt degeneration of neuronal cell bodies by months to years, leading eventually to degeneration of the soma through a process of retrograde degeneration or dying-back pathology.[18,172] In AD and tauopathies, tau hyperphosphorylation and/or dysregulation of tau and the 3R/4R tau ratio affect the binding of tau to microtubules that is in turn associated with altered axonal microtubule dynamics and axonal transport.[13,14,59] Whatever the mechanism and the extent of cytoskeleton collapse in these NDDs, this cellular event likely participates in the process of neurodegeneration through molecular steps that involve the loss of effective axonal transport and the consequent improper subcellular distribution of vesicles and key organelles such as mitochondria, indirectly affecting energy metabolism and synaptic function, although also cytoskeletal abnormalities at the synapse need to be considered.

Notably, neurofilament aggregates are detected in several NDDs.[168,175] Neurofilament aggregates form a liquid crystal gel network in ALS, AD, PD, FTD, SMA, SCA1, and other NDDs.[168,175] Although the mechanism underlying protein

aggregation in these situations remains largely unknown, hyperphosphorylation of intermediate filaments seems to be implicated.[168,175,182] Additionally, aggregation of actin, with a key role in synaptic dynamics, occurs in several NDDs,[95] and likely contributes to neurodegenerative processes. In the last decade, neurofilament concentrations in biofluids have emerged as a promising clinical biomarker for neurodegeneration across many neurological disorders, including ALS, MS, TBI, stroke, and dementias,[182] further underscoring that cytoskeletal defects are a common hallmark of NDDs. Upon degeneration of the affected axon, neurofilaments are thought to be released into CSF and to reach the peripheral blood, where they can be measured at femtomolar concentrations.

Finally, cytoskeletal disruption may interact with other NDD hallmarks, particularly loss of synaptic maintenance and altered energy metabolism, RNA transport, protein aggregation and autophagy,[133] and neuronal death (Figure 3). Release of cytoskeletal proteins (including neurofilament and tau)[182] can induce inflammatory reactions,[183] which can further aggravate existing cytoskeletal defects.

ALTERED ENERGY HOMEOSTASIS

As neurons are highly active and energetically demanding cells of the human body,[98,184] defects in energy metabolism have been shown to participate in many different NDDs[10,11,22,98–100,104,185–191] (Figures 1 and 3). ATP is the key molecule of brain energy metabolism, which can be fueled by glucose or lactate metabolism, and is generated by oxidative phosphorylation in mitochondria via the electron transport chain.[98,186] Energetic substrates (glucose/lactate) can be delivered directly from the blood stream to neurons or indirectly via astrocytes.[98] A direct or indirect impairment in mitochondrial function is involved in the pathogenic process of several NDDs, likely due to low ATP availability and consequent impaired functionality of high energy demanding processes in neurons,[99] particularly at synapses,[97,100] such as ion balance (ATP-consuming membrane pumps), calcium homeostasis, cytoskeletal dynamics, and proteostasis.[98] Moreover, mitochondrial dysfunction can lead to oxidative stress resulting from increased release of free electrons that react with oxygen or nitrogen, giving rise to macromolecular damage via reactive oxygen species (ROS) attack of proteins, lipids and/or nucleic acids.[185–188] Such intracellular alterations can spur on neuronal dysfunction and eventual cell death (Figure 3).

A role of energy homeostasis in neurodegeneration is reflected in stroke where excitotoxicity and energy depletion cooperatively drive neurodegenerative processes.[34,35,86,94,192,193] Similarly, the concomitant effects of axonal injury, excitotoxicity, and energy depletion promote neurodegeneration in SCI.[36,171] Assessment of energy homeostasis can be performed using FDG-PET, which enables to measure regional glucose metabolism in the brain. Altered energy homeostasis is reflected in altered FDG-PET in most, if not all, NDDs.[98] Furthermore, many diseases caused by inherited defects in enzymes of glycolysis, lipid metabolism, or mitochondrial metabolism exhibit symptoms of nervous system malfunction.[185,186,194] Several rare disorders that display neurological defects also arise from mutations in mitochondrial DNA (mtDNA) that impair the functionality of the respiratory chain protein complexes, leading to poor oxygen utilization, oxidative stress, and reduced ATP production.[186,194] Classic mitochondrial syndromes that stem from pathogenic mutations in the nuclear genome, which encodes mitochondrial proteins that perform critical roles in a range of processes including mtDNA maintenance, present with diverse symptoms, including neurological features.[186,194] These clinical observations emphasize the importance of proper mitochondrial integrity and function in supporting the health of organs and tissues, particularly those with high energy demands such as the brain. In addition, several genes linked to NDDs, particularly PD (Parkin, PINK1) and CMT (mitofusin2), have been reported to regulate mitochondrial quality control pathways.[99,104,189,190]

Mitochondrial dysfunction also occurs in several NDDs with non-mitochondrial etiology.[98,99,104,185–188,194,195] For example, studies of preclinical models, patient tissue and NDD patients indicate mitochondrial dysfunction as part of the pathogenic process in AD, HD, and ALS.[104,185,186,191,195–197] Aggregation-prone proteins including α-synuclein and tau modulate actin-dependent mitochondrial fission.[189] As mentioned in the previous section, mutations and aggregating proteins affecting axonal transport and cytoskeletal dynamics can adversely impact mitochondrial transport. Although in most cases, the origin of the mitochondrial dysfunction is unknown, these examples indicate that there are broad mitochondrial problems in NDDs adversely affecting mitochondrial function, quality control, or transport.

The consequences of mitochondrial damage or dysregulation to the cell can be broad (Figure 3). For example, mitochondrial damage can lead to disturbances of the Ca^{2+} homeostasis, resulting in elevated intracellular Ca^{2+} levels and dysregulated Ca^{2+}-dependent enzyme activities, lysosomal enzyme release, and cytoskeletal, protein, lipid and DNA degradation.[198] Reduced mitochondrial function and ATP synthesis is also associated with lower production of the scavenger glutathione (GSH), potentially worsening the oxidative environment of the cell.[199] Impaired mitochondrial function and lower energy supply to neurons also impacts key physiological functions, such as ion homeostasis through the regulation of ion channels; calcium homeostasis, which affects degradation enzymes; cytoskeletal dynamics; and protein and organelle degradation and production pathways. Altered energy homeostasis is therefore tightly linked to several hallmarks, including of neuronal cell death as discussed below.

DNA AND RNA DEFECTS

The accumulation of DNA damage and defects in RNA metabolism have been assigned a critical role in a wide range of NDDs (Figures 1 and 3).[19,44,54,56,57,65,200–208] The genome and transcriptome of cells are susceptible to spontaneous decay and damage by a wide range of intracellular or environmental agents.[65,200–205] In the CNS, the major genotoxins are presumed to be the ROS generated as byproducts of mitochondrial oxidative phosphorylation.[185,187] Persistent alterations in DNA can drive adverse molecular events, such as mutagenesis, chromosome rearrangements, RNA transcription arrest, or DNA

replication fork collapse, events that can promote cell dysfunction and cell death.[202,204,206] To avert these pathogenic endpoints, complex responses and repair systems have evolved to preserve DNA integrity and ensure normal genome functionality.[202,204,206] Similarly, intricate mechanisms exist that faithfully generate, utilize, and process RNA molecules to ensure proper cellular operations. RNA metabolism and homeostasis, which encompass processes such as transcription, RNA splicing, transport and degradation, translation, and the biogenesis of regulatory non-coding RNAs, is a complex collective that involves numerous interactions with RNA-binding proteins and RNA species.[200,201,203,205,208] Abnormalities in any of the components of RNA regulation has consequences on protein translation, protein aggregation, and RNA interference (RNAi).[19,54,56,57,200,201,203,205,208] Defects in RNA metabolism/homeostasis lead to defects in RNA driven processes and RNA transport, as well as to the formation of characteristic stress granules (SGs) that involve ribonucleoproteins (RNPs). In addition, RAN translation (repeat-associated RNA-encoded, non-ATG translation) can lead to the generation of different repeat proteins.[19,28,44,54,56,57,65,200,201,203,205,207–209]

DNA defects

The involvement of DNA damage in neurodegeneration is highlighted by the fact that several rare inherited disorders that exhibit neurological complications result from defects in the ability to efficiently respond to and clear genomic stress.[202,204,209] For instance, mutations in genes that encode proteins that normally operate to resolve DNA double-strand breaks (DSBs) or replicative stress (e.g., ataxia telangiectasia [AT]) can lead to brain atrophy later in life, consistent with endogenous DNA damage promoting progressive neuronal cell loss.[202,209] Several NDDs, mostly recessive ataxias, also originate from inherited defects in the ability to resolve DNA single-strand breaks (SSBs), frequent products of ROS attack of DNA.[210] These SSB repair disorders exhibit strictly neurological phenotypes without cancer predisposition seemingly because elevated endogenous strand breaks result in transcriptional arrest and activation of cell death pathways in non-dividing neurons, whereas SSB damage is cleared faithfully by replication-directed homologous recombination repair in dividing cells. Alternatively, persistent DNA damage promotes cell-cycle activation and reentry, leading to apoptotic cell death of post-mitotic neurons.[211] Consistent with a prominent role for transcription-blocking lesions driving neurological disease, inherited defects in components of the transcription-coupled sub-pathway of nucleotide excision repair (TC-NER) give rise to neurodegeneration.[206] Recessive mutations in senataxin (SETX), an RNA-DNA helicase, are linked to ataxia with oculomotor apraxia type 2 (AOA2), whereas rare dominant mutations are seen in a juvenile-onset form of ALS, implicating genomic R-loops (i.e., RNA-DNA hybrids, frequent intermediates of transcription) in neuronal cell death.[209,212]

Outside of the DNA repair disorders noted above, defects in DNA damage processing have been connected to many other NDDs, including sporadic and familial cases of AD, PD, HD, and ALS.[202,213,214] In all situations, increased oxidative DNA damage, often arising in concert with mitochondrial dysfunction, has been shown in disease tissue. Evidence suggests that compromised repair of oxidative DNA damage may be a risk modifier for neurological degeneration in AD models and PD-like pathology.[215–217] There is also evidence that DNA DSBs accumulate in vulnerable neuronal and glial cell populations from early stages onward in AD, possibly due to reduced expression of key DSB response proteins.[202,213,214,218] Furthermore, proteins associated with tauopathies (tau), ALS/FTD (TDP-43 and FUS), HD (Htt), spinocerebellar ataxia (ATXN2), or SMA (SMN1/SNM2) participate in various DNA damage responses, most commonly in the context of DNA strand breaks.[202,219] Interestingly, aggregates of α-synuclein can activate the DSB response kinase mutated in AT (i.e., ATM), whereas elevated levels of poly(ADP)ribose, a product of poly(ADP-ribose) polymerase 1 (PARP1) hyperactivity, accelerates the fibrillization of α-synuclein.[220] Recent evidence also indicates that the accumulation of nuclear DNA damage leads to hyperactivation of the DNA damage sensor PARP1, consequent NAD consumption, and mitochondrial dysfunction.[221]

RNA defects

Accumulating data indicate an important role for RNA dysregulation in several NDDs, by altering physiological functions or by inducing RNA toxicity or formation of SGs that involve protein aggregation.[19,26,28,44,54,56,57,65,201,207,208] For example, RNA defects play a role in the disease etiology of ALS/FTD and polyQ diseases.[28,44,53,54,56,57,65] Mislocalized TDP-43, which functions as an RNA-binding protein, causes altered RNA splicing, RNA stability, and RNA transport.[53] Similarly, pathogenic mutations in FUS cause mislocalization of the normally nuclear protein to the cytoplasm, leading to defects in RNA metabolism, specifically of transcripts encoding proteins regulating dendritic growth and synaptic functions.[222] RNA metabolism defects are also linked to *C9orf72* linked FTD/ALS.[28,44,56,57,223,224] In polyQ diseases, both CAG expansions, which can cause aberrant sequestration of proteins, and RAN translation, which leads to the generation of repeat proteins, are considered key pathogenic elements through the entrapment of key regulatory proteins. Additional examples supporting RNA defects as a driving mechanism in NDDs include multisystem proteinopathy (MSP), caused by mutations in the heterogeneous nuclear RNP A1 (HNRNPA1) or A2B1 (HNRNPA2B1) gene, and SMA, as SMN1/SMN2 are transacting factors involved in splicing.[225]

The formation of SG cytoplasmic aggregates is also thought to play an important role in the NDD process.[200,207,208] SGs are dense cytosolic RNP complexes that are formed in response to cellular stress to temporally inhibit translation and store mRNAs. Several RNA-binding proteins associated with FTD and ALS (i.e., TDP-43, FUS, EWSR1, TAF15, hnRNPA1, hnRNPA2B1, ATXN2, TIA1, and VCP) are involved in SG dynamics.[207,208] Moreover, arginine-containing DPRs can alter SG composition and dynamics.[223,224] SG formation can be induced by dysfunctional UPS, culminating in the accumulation of ubiquitinated proteins.[54,200] Thus, changes in RNA metabolism are associated with altered proteostasis, another hallmark of NDDs.

Some NDDs involving microsatellite repeat expansion may in part originate from sequestration of RNA-binding proteins.[19,28,44,201] For example, transcription of an expanded

CTG triplet in the 3′ UTR of the *DMPK* gene in myotonic dystrophy leads to synthesis of repeat-containing RNA that forms aggregates and RNA foci, sequestering RNA-binding proteins with critical functions in alternative splicing.[54] A similar phenomenon is observed in the repeat-associated disorders, Fragile X-associated tremor/ataxia syndrome (FXTAS) and ALS/FTD.[54,205] Collectively, altered RNA homeostasis is linked to altered protein production and protein aggregation, and SG formation leads to protein sequestration that impairs functionality, including of proteins that maintain synaptic function. With links already presented between RNA metabolism/homeostasis and other NDD hallmarks (e.g., mRNA axonal transport, local protein generation at synapses, energy homeostasis, and proteostasis[54]) (Figure 3), it is evident that these molecular processes can impact one another.

INFLAMMATION

Neuroinflammation, including microgliosis and astrogliosis, is a pathological hallmark of NDDs, including AD, PD, ALS, HD, and stroke[37,38,40,110,183,226,227] (Figures 1 and 3). Besides the invariable presence of inflammation in postmortem brain samples of NDD patients, a definitive role of neuroinflammation in neurodegeneration is demonstrated in the prototypic neuroinflammatory disease, MS and related NDDs.[228] As the well-characterized neuroinflammatory component of these diseases is reviewed elsewhere,[37,38] we focus on the contribution of inflammation in NDDs, thereby classifying it as an NDD hallmark.[4,7,40,55,106,110,183,226–230]

Microgliosis is invariably detected in all NDDs, including proteinopathies as well as non-proteinopathies.[110,183,228] Microglia normally exert sensor, housekeeping, and defense functions in the brain,[183,228] and aberrations in these functions can lead to neurodegeneration. In defending brain function, microglia typically react to pathogens or signs of injury. Upon activation, microglia are involved in cytokine/chemokine production, phagocytosis activation, dysregulation of physiological functions, and ROS production. After an acute stressor, the inflammatory process is normally actively resolved. However, failure to resolve results in chronic inflammation that can promote the neurodegenerative process.[183,228] Unresolved activation of microglia may occur in NDDs due to the presence of danger signals, such as protein aggregates, misfolded proteins, damaged synapses, Ca^{2+} influx, or mitochondrial ROS, i.e., mechanisms driving other NDD hallmarks. Several aggregated NDD proteins induce microglial activation, such as Aβ, tau, α-synuclein, PrP fibrils, or SOD1.[230–233] Moreover, a transition between different microglial states is believed to occur during the disease process, with particular populations specifically associated with neurodegeneration (e.g., disease-associated microglia [DAM] or microglial neurodegenerative phenotype [MgND]).[232,233] These microglial populations elicit unique roles in the regulation of cytokine production, phagocytosis, ROS production, or astroglial interactions, ultimately impacting synaptic function and neuronal cell death. Insights into the detrimental and protective roles of the different microglial populations will be important for effective therapeutic targeting in NDDs.[228,229]

An active role of microglia in NDDs is also supported by genetic studies. For example, a crucial role for microglia was revealed by the identification of *triggering receptor expressed on myeloid cells 2 (TREM2)* loss-of-function mutations in individuals with Nasu-Hakola disease,[228,234] a rare disorder associated with neurodegeneration leading to dementia and premature death. As TREM2 is only expressed in microglia in the brain, these cells must contribute to the CNS degeneration in this disorder.[234] *TREM2* genetic variants are also associated with risk for AD in the heterozygous state,[235,236] and TREM2, in concert with apolipoprotein E (ApoE), plays a crucial role in the transition of homeostatic microglia to microglia associated with disease phenotypes.[232,233,237] Indeed, both ApoE and TREM2 modify protein aggregation and neurodegeneration in preclinical models of NDDs. TREM2 function appears to be protective against Aβ-related local toxicity, whereas later in the tauopathy phase of disease, its function may be detrimental.[238,239] ApoE, acting through microglia, plays an important role in driving tau-mediated neurodegeneration.[240,241] Along the same lines, GRN expression increases microgliosis and synaptic pruning, leading to hyperexcitability.[108,158] Interestingly, Htt is also strongly expressed in microglia, and expression of mutant Htt in microglia promotes autonomous microglial activation and is associated with increased neurodegeneration.[242]

Genome-wide association studies in AD have identified many genes important to microglia function, endocytosis, and lipid metabolism.[3,9] A close relationship between lipid metabolism and microglial activation is emerging as lipid related genes are upregulated in the transition from homeostatic to damage-associated microglia.[232,233] Additionally, there is genetic evidence for microglial contributions to sporadic synucleinopathies.[243] As in AD, ApoE acts as a risk factor for dementia in the context of Lewy body disease,[243] and there is evidence that ApoE is involved in synuclein-mediated neurodegeneration.[244] GRN is also a shared genetic risk factor for multiple NDDs, including PD.[245] Finally, LRRK2 is expressed in microglia, where it has been proposed to modify the risk of sporadic PD.[246] As a consequence, microglia could contribute to the pathogenesis of multiple NDDs. That this association is causal for neurodegeneration and not simply a bystander effect is supported by studies in preclinical models, for example in transgenic $SOD1^{G37R}$ mice, where it was observed that the neurodegenerative process is considerably delayed by removing mutant SOD1 from macrophages and microglia.[247] Moreover, microglial elimination via CSF1R inhibition modifies progression in models of AD,[248] tauopathies,[249] PrD, and TDP-43 ALS.[250]

Notably, microglia closely interact with and activate astrocytes, which are also critical for the maintenance of neuronal health and function.[106,251–253] An active role of astrocytes in the neurodegenerative process of several NDDs has emerged and has been discussed in detail elsewhere (reviewed in Phatnani and Maniatis,[251] Sofroniew and Vinters,[252] and Sofroniew[253]). Briefly, astrocytes are crucial for proper neuronal functioning and exert a key role in preserving glutamate homeostasis and are a vital part of the tri-synaptic network.[98,106] Astrocytes release extracellular factors, including chemokines and cytokines,[106,251,252] and play a key role in glial scar formation. By modulating these different processes, astrocytes can directly contribute to synaptic defects and neurodegeneration in a non-cell-autonomous fashion (Figure 3). Importantly, astrocytes are

typically activated in the proximity of damaged neurons, leading to reactive gliosis. Astrocytes may also be a direct target of protein aggregation pathology in some NDDs. A close reciprocal signaling network between astrocytes and microglia exists as well.[106,251,252] Fluid biomarker and PET-imaging studies have been used to detect and monitor glial contributions to NDDs, including applications involving microglia-specific PET ligands[254] and CSF- or blood-based biomarkers such as glial fibrillary acidic protein (GFAP), TREM2, and certain cytokines.[255] These studies have revealed tight, disease stage-specific links between glial activation and the NDD process.[256]

Finally, inflammation, i.e., reactive astrocytes and reactive microglia, activated by and interacting with the different NDD hallmarks, may work in combination with other NDD hallmarks to accelerate the disease process (Figure 3). As outlined above astrocyte activation affects synaptic function, energy homeostasis, protein aggregation, and neurodegeneration, while reciprocally modulating microglia.[106,251–253] Conversely, overactive microglia play a role in synapse elimination in NDDs, potentially contributing to neuronal network dysfunction.[106–108] As described above, microglial activation by protein aggregation and the role of microglia in affecting protein aggregation are well established, indicating an adverse interaction between these two phenomena.[230,231] In response to danger signals, microglia secrete ROS, adding to oxidative damage and altering energy homeostasis in the brain.[187] Microglia remove neurons expressing eat-me signals at the cell surface.[257] These examples highlight the close interconnection between inflammation and other NDD hallmarks.

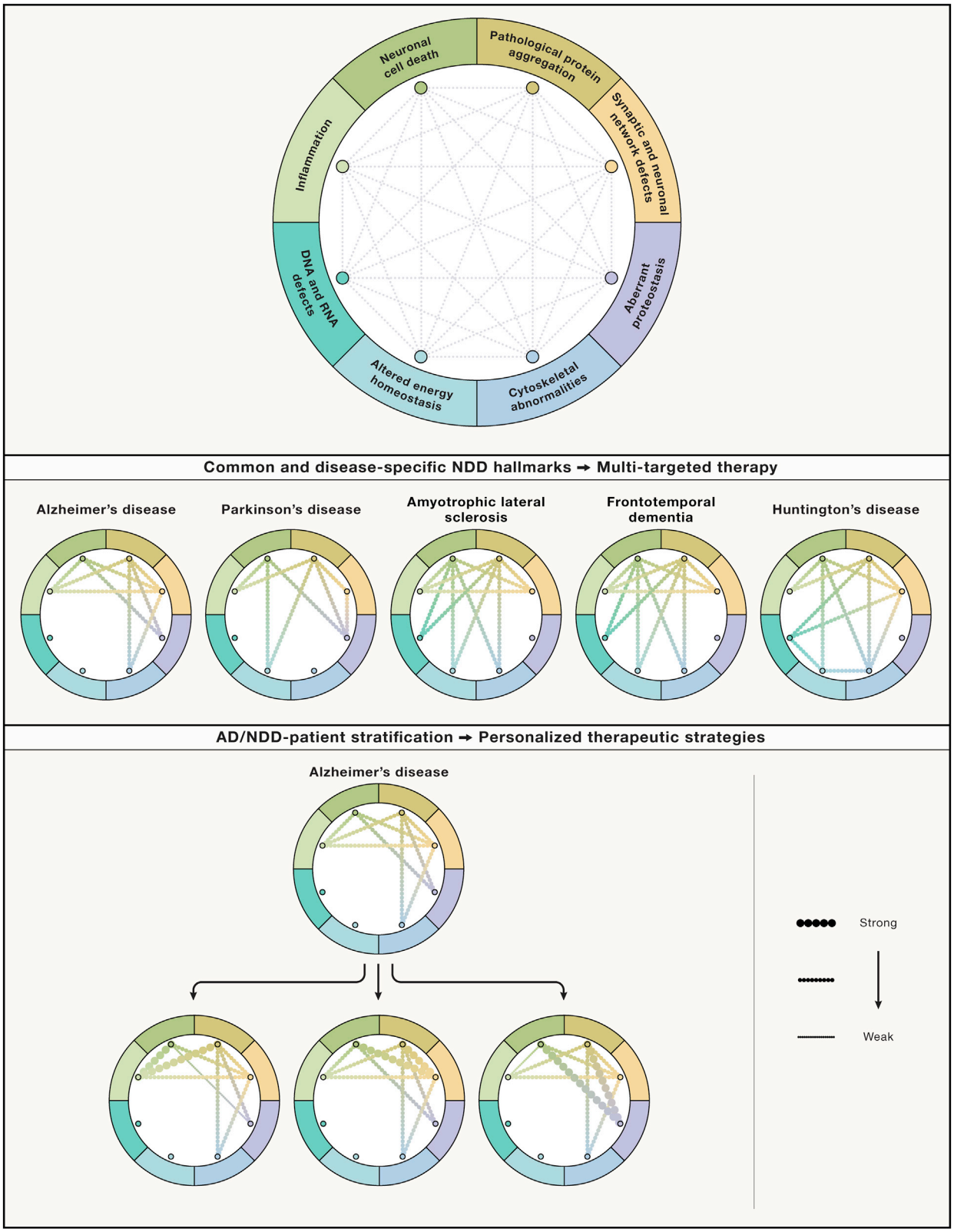
NEURONAL CELL DEATH

Several inherent properties of neurons may make them especially vulnerable to cell death in NDD (Figures 1 and 3). These include: (1) their post-mitotic nature resulting in (a) the gradual accumulation of age-associated damage to DNA, lipids, proteins, and organelles and (b) the inability to replicate and replenish the neural cell population; (2) their high energy requirements, mainly due to the need to support synaptic function, and the associated ROS production via mitochondrial oxidative phosphorylation; (3) their extended axons and dendrites, leading to a requirement for transport and structural organization over long distances; and (4) their dependence on glial cells for maintenance, energy, and defense. As a result, neurons appear to be more susceptible to cell death, a characteristic that is exacerbated by an age-associated decline in resilience mechanisms. The above-described NDD hallmarks individually and collectively contribute to neuronal cell loss, presumably in a manner that gives rise to distinct pathological and clinical manifestations. We propose that different NDD hallmarks act in concert to ultimately override intrinsic neuronal resilience to internal and external insults (Figure 3).

Neuronal death, which ultimately results in brain volume loss that can be monitored using volumetric MRI and in release of intraneuronal proteins such as tau and neurofilaments into biofluids, comes in different forms. Specific classification can be made based on the mechanism of death or the inducer of death, as reviewed before.[114,139,140] The best-described mechanisms of neuronal death include intrinsic and extrinsic apoptosis and necrosis, but others including necroptosis, ferroptosis, phagoptosis, autophagic cell death, pyroptosis, and mitochondrial permeability transition are also well documented.[114,139,140] Although different types of neuronal death exist, there is crosstalk between mechanisms, and it is possible that if a neuron does not execute a specific cell death program, another one might take over. Many of the immediate triggers for neuronal cell death have been mentioned already and include: axotomy, aberrant cell-cycle reentry, glutamate excitotoxicity and oxytosis, loss of connected neurons, aggregated proteins, the unfolded protein response (UPR), lysosomal rupture, autophagy, oxidants, and macromolecular (DNA) damage. Thus, multiple NDD hallmarks discussed in this review are inducers of neuronal cell death and are expected to synergistically drive the neurodegenerative process (Figure 3).

Insight into the molecular players and pathways involved in cell death are important for understanding mechanisms of neurodegeneration. Excitotoxicity causes neuronal death by excess cytoplasmic Ca^{2+}, activating various programs of neuronal death by opening of the mitochondrial permeability transition pore (mPTP) and activating calpains that promote apoptosis or necrosis by lysosomal cell death.[114] Energy depletion causes neuronal cell death by a different mechanism, where deprivation of oxygen and glucose results in rapid ATP depletion in neurons leading to plasma membrane depolarization and subsequent activation of presynaptic and somatodendritic voltage-dependent Ca^{2+} channels and the release of glutamate. Cell death pathways can also be initiated directly by mitochondrial damage and associated mitochondrial dysfunction. For instance, upon disruption of mitochondrial integrity, the apoptosis inducing factor (AIF) can be translocated from mitochondria to the nucleus and induce caspase-independent chromatin condensation and DNA cleavage.[114,139,140] Additionally, upon permeabilization of the outer mitochondrial membrane, cytochrome *c* (CytC) can be released, resulting in the generation of an apoptosome complex containing CytC, caspase-9, and apaf-13. This mitochondrial-associated process can be induced by several cellular stressors, including DNA damage, oxidative stress, glucocorticoids, ceramide production, or loss of growth factors.[114,139,140] Lysosomal permeabilization is both induced by and contributes to altered cellular proteostasis and aberrant protein aggregation of characteristic, disease-associated proteins. Lysosomal rupture leads to neuronal cell loss by release of lysosomal enzymes, including cathepsins and hydrolases.[114,139,140]

In addition to the cell-autonomous death pathways, non-cell autonomous processes have been demonstrated to contribute to neuronal loss. For example, apoptotic cells can be phagocytosed by activated microglia, thereby limiting ongoing neuroinflammation (Figure 3). Apoptotic neurons are tagged for phagocytosis by exposing phosphatidylserine (PS) as an eat-me signal. In normal physiological conditions, PS is not accessible, although during apoptosis, caspase-dependent cleavage of the PS transporters results in cell surface exposure of PS.[114] Interestingly, PS exposure was recently demonstrated to occur in neurons displaying pathological tau forms, contributing to neuronal loss.[258] Thus, protein aggregation and non-cell autonomous cell death pathways interact. Undoubtedly, NDD



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hallmarks converge on neuronal death, as the final stage of NDDs is the loss of the neuronal cell population leading to impaired functionality.

HALLMARKS OF NDDs: A FRAMEWORK FOR A HOLISTIC APPROACH TO STUDY NDDs

Following, we provide a framework for a holistic approach for studying NDDs and unifying and categorizing different NDDs based on their primary NDD hallmarks. We provide this framework as a summation of the genetic factors and biochemical pathways that contribute to NDDs, uncovering overlapping processes between NDDs. We have made the case specifically for eight common hallmarks of NDDs: pathological protein aggregation, synaptic and neuronal network dysfunction, aberrant proteostasis, cytoskeletal abnormalities, altered energy metabolism, DNA and RNA defects, inflammation, and neuronal cell death.

The interconnectedness of NDD hallmarks highlights the need for multi-targeted therapies

An important insight from this discussion is that the different NDD hallmarks show a high degree of interconnectedness (Figure 4). For example, synaptic dysfunction and excitotoxicity are closely linked to energy homeostasis, oxidative stress, and neuronal death. Direct relations between pathological protein aggregation, aberrant proteostasis, synaptic function, excitotoxicity, and neuronal death have also been identified. Similarly, energy homeostasis, oxidative stress, DNA damage, and neuronal death are highly interactive processes. Non-cell autonomous pathways involving glia are important in the modulation of neuronal function, synapse elimination, neurodegeneration, and neuroinflammation. These examples highlight the close links between and the interconnectedness of the hallmarks, suggesting that neuronal resilience to insults may be overridden by the adverse effects of simultaneous and synergistic events that promote neuronal death.

The interconnectedness of NDDs should be considered in therapeutic strategies as such interactions imply that targeting a single NDD hallmark may be insufficient to halt the neurodegenerative process. When targeting only one NDD hallmark, the disease process may be overtaken by one of the other hallmarks, suggesting a necessity for combinatorial multi-target therapies to effectively halt NDDs. Although promising anti-sense oligonucleotide (ASO)-based therapies have been identified that use direct genetic silencing of a defective gene in cases of SMA, therapies for sporadic diseases remain elusive. We propose that one approach going forward would be to tune any patient's treatment based on the individual's most prominent hallmarks as determined by multimodal biomarker panels, targeting multiple systems concomitantly during the therapy, as discussed below.

A framework for identifying commonalities and diversification between and within NDDs

Despite the similar hallmarks for NDDs, their relative importance in the different diseases clearly differs, likely dictated by genetic and environmental factors as well as by specific neuronal populations, brain regions, or cell types affected. In this respect, it will be important to define the primary and main disease pathway contributors and to pinpoint the more secondary effects for each specific NDD (Figure 4A) and even within subcategories of NDDs (Figure 4B). For example, pathological protein aggregation and aberrant proteostasis, synaptic defects, and inflammation could be considered major contributors to AD, whereas aberrant proteostasis combined with mitochondrial defects and disturbances in energy metabolism may play important roles in PD (Figure 4A). Cytoskeletal abnormalities that manifest in axonal disturbances appear to be primary in peripheral neuropathies. Conversely, inflammation is a clear, primary contributor in the prototypic inflammatory diseases, such as MS. In ALS, a combination of protein aggregation and RNA or DNA metabolism defects, combined with synaptic and neuronal network defects seems to be crucially involved. PrDs are classic examples of diseases in which protein aggregation and propagation are key pathogenic processes. However, neuronal dysfunction and cell death is probably induced by a combination of NDD processes that synergistically drive neurodegeneration. Besides the obvious differences between NDDs, their commonalities may suggest that some strategies might have broader applications across the spectrum of NDDs and might be useful for targeting multiple shared NDD hallmarks. However, disease-specific aspects need to be considered.

A framework for stratification of subtypes within specific NDDs for clinical trials

Importantly, the proposed framework provides a basis for stratification not only across NDDs, but also of subtypes within specific NDDs (Figure 4B). Individual/personalized differences in the primary drivers clearly exist within specific NDDs. These differences are defined by genetic factors, reflected in polygenic risk score, but also by non-genetic factors including age, lifestyle practices, and environmental exposures. Differences in resilience and neuronal vulnerability of the different brain regions in NDDs but also and particularly among individuals within a specific NDD, will determine the combined primary NDD hallmarks that drive the disease process. Heterogeneity among patients within specific NDDs may contribute to the failures of clinical trials that target one particular NDD hallmark, pointing to the need for stratification of patients. Importantly, the pathologies underlying many of these diseases start many years before clinical symptoms. By the time symptoms emerge, significant neuronal and synaptic loss is already present. Identification of individuals in the pre-symptomatic stages of disease via the use of

Figure 4. Hallmarks of NDDs and their interconnectedness as a framework for categorizing NDDs and identifying subtypes within NDDs, as a basis for personalized, combinatorial, and multi-targeted therapies to effectively halt NDDs

(A) The interconnectedness of the hallmarks is schematically presented, providing a framework for a holistic approach to study NDDs. This framework enables categorizing NDDs based on their primary hallmarks (A) examples are presented for common NDDs, i.e., AD, PD, ALS, FTD, and HD.

(B) In addition, this framework enables identifying subtypes of patients within specific NDDs, enabling patient stratification based on their primary hallmarks (B). These are defined by the NDD insult, and by neuronal resilience and vulnerability of the individual. Shown are examples of subtypes within AD. Hence, NDD treatment strategies can be designed based on individual hallmark profiles, enabling designing personalized, multi-targeted therapies.

biomarkers will be critical for primary and secondary prevention trials. Different subtypes of NDDs, based on molecular profiles, may present with similar symptoms; however, genetic and external factors may shift the weight and relative contribution of the different NDD hallmarks within a given NDD. For instance, within AD, there likely exist patients that besides the strong protein aggregation component display a strong inflammatory component, a strong synaptic component, or a strong proteostasis/(ALP/UPS) component, with each subtype likely benefiting differently from a particular (multi-targeted) therapy (Figure 4B). The NDD hallmarks may therefore provide a framework for patient stratification within NDDs, defining subtypes for the design of personalized, multi-targeted therapies (Figure 4B).

Taken together, we provide a framework for unifying and categorizing NDDs, as well as for stratification of subtypes and patients within specific NDDs, based on NDD hallmarks identified by decades of genetic and biochemical investigations in models and patients. We propose that effective halting of NDDs will require improved biomarkers for NDD hallmarks and multi-targeted personalized therapies, due to the interconnectedness between NDD hallmarks.

ACKNOWLEDGMENTS

This work was supported in part by the National Institutes of Health, National Institute on Aging, Intramural Research Program (M.R.C.). Research from L.V.D.B. is supported by VIB, the KU Leuven, the Fund for Scientific Research Flanders (FWO-Vlaanderen), the Agency for Innovation by Science and Technology (IWT; SBO-iPSCAF), the Thierry Latran Foundation, the Muscular Dystrophy Association (MDA), the ALS Association (ALSA), the Association Française contre les Myopathies (AFM), the Association Belge contre les Maladies Neuro-Musculaires (ABMM), Target ALS, and the ALS Liga België (A Cure for ALS). D.M.W. is supported by Stichting Alzheimer Onderzoek (SAO-FRA Belgium). H.Z. is a Wallenberg Scholar supported by grants from the Swedish Research Council (#2018-02532), the European Research Council (#681712), Swedish State Support for Clinical Research (#ALFGBG-720931), the Alzheimer's Drug Discovery Foundation (ADDF), USA (#201809-2016862), the AD Strategic Fund and the Alzheimer's Association (#ADSF-21-831376-C, #ADSF-21-831381-C, and #ADSF-21-831377-C), the Olav Thon Foundation, the Erling-Persson Family Foundation, Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (#FO2019-0228), the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement no 860197 (MIRIADE), the European Union Joint Programme – Neurodegenerative Disease Research (JPND2021-00694), and the UK Dementia Research Institute at UCL (UKDRI-1003). D.M.H. is supported by NIH grants RF1AG047644, RF1NS090934, RF1AG061776, and U19AG069701, the Cure Alzheimer's Fund, and the JPB Foundation. I.D.W. is supported by Stichting Alzheimer Onderzoek (SAO-FRA Belgium) and Fonds Wetenschappelijk Onderzoek - Vlaanderen (FWO)—research project no. G0C6819N and BOF funding UHasselt (Methusalem). We apologize for omission of key-publications in the field. Many elegant studies have directed the field, and although we would have liked to refer to all these publications, this was not possible, due to the breadth of the topic and the limitations in number of references. This article is dedicated to all that have been or are affected by NDDs and to their caregivers, who are combating NDDs daily, hourly. This article aims at joining their fight against NDDs.

DECLARATION OF INTERESTS

D.M.H. is a co-founder with equity in C2N Diagnostics. He consults for C2N Diagnostics, Genentech, Denali, Cajal Neurosciences, and Alector. H.Z. has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Passage Bio, Pinteon Therapeutics, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). L.V.D.B. is head of the Scientific Advisory Board of Augustine Therapeutics (Leuven, Belgium) and is part of the Investment Advisory Board of Droia Ventures (Meise, Belgium). L.V.D.B. has a patent on the use of HDAC inhibitors to treat CMT disease (Serial No. 61/404,796).

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