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Converging pathways in neurodegeneration, from genetics to mechanisms

Li Gan[1,2,*], **Mark R. Cookson**[3,*], **Leonard Petrucelli**[4,*], and **Albert R. La Spada**[5,*]

[1]Gladstone Institutes, University of California, San Francisco, CA, USA

[2]Feil Family Brain and Mind Research Institute, Weill Cornell Medicine, New York, NY, USA

[3]Cell Biology and Gene Expression Section, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA

[4]Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA

[5]Departments of Neurology, Neurobiology, and Cell Biology, and the Duke Center for Neurodegeneration & Neurotherapeutics, Duke University School of Medicine, Durham, NC, USA

Abstract

Neurodegenerative diseases cause progressive loss of cognitive and/or motor function and pose major challenges for societies with rapidly aging populations. Human genetics studies have shown that disease-causing rare mutations and risk-associated common alleles overlap in different neurodegenerative disorders. Here we review the intricate genotype-phenotype relationships and common cellular pathways emerging from recent genetic and mechanistic studies. Shared pathological mechanisms include defective protein quality-control and degradation pathways, dysfunctional mitochondrial homeostasis, stress granules, and maladaptive innate immune responses. Research efforts have started to bear fruit, as shown by recent treatment successes and an encouraging therapeutic outlook.

Neurodegenerative diseases cause progressive loss of brain functions and overlapping clinical syndromes. For example, cognitive deficits occur not only in Alzheimer's disease (AD), but also in vascular dementia, frontotemporal dementia (FTD), mixed dementia, and dementia with Lewy bodies (LBD). Similarly, the motor system is affected in amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), Parkinson's disease (PD), and spinocerebellar ataxias (SCAs). In all of these diseases, aging is a common risk factor. Thus, as life expectancy rises worldwide, the prevalence of these devastating diseases will increase, imposing an onerous socioeconomic burden on patients, families, and communities[1,2].

Correspondence should be addressed to L.G. or M.R.C. or L.P. or A.R.S.
*lig2033@med.cornell.edu; cookson@mail.nih.gov; petrucelli.leonard@mayo.edu; al.laspada@duke.edu

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Despite their diverse clinical manifestations, reflecting loss of specific neurons and synapses in distinct brain regions (Fig. 1), neurodegenerative diseases share common features and mechanisms. One such feature is regional aggregation of cytosolic or nuclear proteins[3]. These include beta-amyloid (Aβ) plaques in AD, inclusions of hyperphosphorylated microtubule-binding tau in AD and other tauopathies, aggregates of α-synuclein in PD and other synucleinopathies, inclusions of TAR DNA-binding protein (TDP)-43 in ALS and FTD, and polyglutamine protein aggregates in HD and other CAG-polyglutamine repeat diseases. Moreover, some aggregates seed and spread from one region to another, consistent with the progressive nature of neurodegenerative diseases[4].

Tremendous advances have been made in dissecting the molecular underpinnings of neurodegenerative disease. We begin by reviewing progress made and lessons learned from human genetic studies of rare mutations and more common risk alleles and their complex relationship with neurodegenerative phenotypes. We then summarize shared mechanisms of neurodegeneration, highlighting defects in protein quality control and degradation mechanisms, mitochondrial homeostasis, stress granules, and synaptic toxicity, and we discuss maladaptive innate immune responses as pathogenic drivers of neurodegenerative diseases. We close with a brief update on current and emerging therapies.

Complex genotype-phenotype relationships

Human genetic studies have deepened our understanding of neurodegenerative conditions. Early successes came from studying single-gene disorders, such as HD and other triplet repeat expansions, including X-linked spinal and bulbar muscular atrophy and SCAs. Cloning of the genes for AD, ALS, PD, and related conditions revealed that multiple genes give rise to similar clinical entities. For example, dominant mutations in amyloid precursor protein (APP), presenilin 1 (PS1), and PS2 all result in early-onset AD[5]. Similar observations with different genes have been made for PD and ALS[6]. Identifying these genes has elucidated disease pathways and, in some cases, suggested therapeutic interventions.

In genetic studies, the most informative families have high penetrance of the mutation and consistent phenotypes in affected individuals. Since phenotypes are mapped to chromosomal regions by co-inheritance of marker variants, ideally only individuals with the mutation have the disease. However, this ideal correspondence of mutation and phenotype is often absent because the expressivity of disorders can vary within families. For example, hexanucleotide repeat expansion mutations in intron 1 of *C9ORF72* causes ALS in some family members and FTD in others[7,8]. Moreover, the neuronal types affected are spatially, developmentally, and evolutionarily distinct. ALS affects motor neurons in the ventral horn of the spinal cord, whereas FTD affects pyramidal neurons in the frontal and temporal lobes of the cerebral cortex[9]. Thus, a neurodegenerative process evoked by a mutation can cause a spectrum of clinical signs.

Neurological phenotypes can also vary within a family. For example, expanded SCA triplet repeats usually cause ataxia due to loss of cerebellar Purkinje cells, but SCA2 and SCA3[10] mutations can cause Parkinsonism. Sometimes both phenotypes are present. Indeed, most SCA2/3 cases have severe loss of dopaminergic neurons in the substantia nigra pars

compacta, which is typical of PD, but not all patients have clinical Parkinsonism, possibly because other neurons in these motor circuits are damaged[11]. Therefore, like ALS–FTD mutations, SCA2/3 expansions affect many types of neurons, suggesting that overlapping mechanisms contribute to different diseases.

Neuropathologically, some mutations cause similar clinical events despite differences in protein deposition. For example, although mutations in *LRRK2* cause clinically uniform PD[12,13], patients may have α-synuclein$^+$ Lewy bodies, tau deposition, or no protein deposition pathology whatsoever[12]. Thus, protein deposition and clinical signs, presumably driven by neuronal damage in different regions, can be dissociated from each other, and common mechanisms can have diverse pathological and clinical outcomes.

Genetic variation also contributes to sporadic neurodegenerative diseases, in which common risk single-nucleotide polymorphisms (SNPs) have been identified by genome-wide association studies (GWAS). Disorders with overlapping pathologies tend to share genetic risk loci. For example, *SNCA*, an important risk locus in PD, encodes the major deposited protein in the disease, α-synuclein[14]. α-Synuclein is also deposited in glial cells in multiple system atrophy (MSA) and in cortical regions in diffuse LBD, and GWAS have identified signals in the same chromosomal region for MSA[15] and LBD[16]. Furthermore, LBD shares some genetic risk with both AD[17] (including the major AD risk gene, *APOE*[18]) and PD.

GWAS generally identify genomic regions rather than single genes because, owing to linkage disequilibrium, individuals inherit large blocks of chromosomes from each parent. Therefore, caution is warranted in concluding from GWAS data that a particular gene is involved in a disease. Furthermore, a chromosomal region may include more than one functional variant. While PD, LBD, and MSA all have signals around *SNCA*, a gene nominated by GWAS, different variants are most strongly associated with each disease and might have subtly different effects on α-synuclein expression and splicing.

Similarly, tauopathies such as progressive supranuclear palsy and corticobasal degeneration also share genetic risk, including the *MAPT* locus[19,20]. Perhaps more surprisingly, PD risk is also influenced by *MAPT* variants[21], but there is no equivalent signal in AD, which is also a tauopathy. Thus, there is no simple relationship between a genetic risk factor and the deposited protein, although some proteins, such as α-synuclein and tau, are clearly relevant to both.

Variants identified by GWAS tend to have small individual effects on risk, but their cumulative effects can alter the functions of genes organized in pathways. Analysis of GWAS risk data in AD has identified pathways associated with cholesterol metabolism and complement activation[22]. These categories, particularly immune signaling, are further supported by network analysis of postmortem AD brains[23]. GWAS have also identified an immune component of PD risk based on cytokine activation[24], despite little overlap in disease SNPs between PD and AD[25]. Thus, although initial event may vary in different diseases, common pathways may be affected as these diseases progress.

GWAS has also been used to study Mendelian disorders. Specifically, in HD, the age of onset usually correlates negatively with the length of the triplet repeat, chromosomal regions

that increase or diminish age-at-onset have been identified, and pathway analysis shows enrichment in DNA repair pathways[26]. This is of particular interest because DNA repair deficiency causes other neurological disorders, including complex ataxia syndromes[27]. The notion that Mendelian and sporadic neurological diseases share mechanisms is supported by the overlap of the clinical spectrum of idiopathic and inherited diseases, such as the phenotypic similarity between sporadic PD and the disease in LRRK2-mutation carriers[28,29].

However, there are more complex and interesting situations. For example, homozygous mutations in *GBA* cause the early-onset lysosomal storage disorder Gaucher's disease, whereas heterozygous mutations increase risk for PD[30,31]. In fact, multiple lysosomal storage disorder alleles contribute to risk for sporadic PD[32], and GWAS found enrichment of variants around several lysosomal genes in the same disorder[14].

Even when distinct genetic variants are associated with different diseases, common biological themes are likely. This observation may reflect use of the term 'disease' to describe syndromic disorders that differ in molecular etiology. In other words, genetic risks may overlap because classification by disease is somewhat artificial. However, not all neurodegenerative diseases have the same mechanism(s), as there are unique aspects to genetic risk. We will next discuss shared mechanisms of neurodegeneration, even in syndromes that are clinically distinct.

Alteration of common neuronal pathways

Unlike other cells in the nervous system, neurons cannot divide. Neurons face additional challenges, including a continuous demand for high levels of energy, maintenance of protein and organelle quality control, rapid delivery of molecules within and out of cells, and trafficking of organelles and other factors over considerable distances within the cell. Impairment of the pathways responsible for these functions can lead to neurodegeneration.

Many neurodegenerative disorders are characterized by the accumulation of misfolded proteins or peptide fragments in the brain and spinal cord. Indeed, disease genes underlying strictly inherited forms of AD, PD, and ALS give rise to disease-specific protein inclusions[3]. The existence of similar inclusion bodies in patients with inherited and sporadic neurodegenerative diseases suggests overlapping disease mechanisms, supporting the view that therapies directed at shared pathobiology will be effective for both inherited and sporadic diseases. We will focus on the following neuronal pathways altered in various neurodegenerative diseases: protein folding and quality control, autophagy and lysosomal dysfunction, mitochondrial damage and homeostasis, protein seeding and propagation, stress granules, and synaptic toxicity (Fig. 2). Dysfunctional nucleocytoplasmic transport and unconventional translation in neurodegeneration are discussed in excellent reviews[33,34].

Protein quality control.

Since protein misfolding is a key pathogenic mechanism in neurodegenerative disease, it is important both to understand how protein quality control pathways respond to misfolded proteins and to define their effects on the proteostasis network. In all organisms, molecular

chaperones regulate protein folding, including the heat-shock proteins (Hsps; Fig. 2). In mammals, Hsp40 and Hsp70 typically promote turnover of neurodegenerative disease proteins through the ubiquitin-proteasome system, whereas Hsp90 may paradoxically stabilize misfolded disease-causing proteins[35]. Although these endogenous systems reduce toxicity, an additional approach for therapies would be to 'disaggregate' misfolded proteins and return them to their natively folded and functional state (Fig. 2).

Yeast express the protein disaggregase Hsp104, but multicellular organisms lack an Hsp104 ortholog. Attempts to deliver Hsp104 to cells and organisms expressing neurodegenerative proteins and to create more potent variants for therapeutic use have yielded promising results[36], suggesting that sequence modifications of endogenous metazoan Hsp110, Hsp70, Hsp40, or HtrA1 might convert them into disaggregases[37]. Another emerging theme in molecular chaperone research is the potential role of heat-shock transcription factor (HSF) dysregulation in neurodegenerative disease. HSF1 controls the expression of numerous molecular chaperones, and impaired HSF1 function has been implicated in HD, AD, PD, and ALS[38]. In HD, HSF1 dysfunction increased expression of casein kinase 2 subunit α' (CK2 α') and of an E3 ligase F box component (FBXW7), thereby increasing the phosphorylation and ubiquitin-dependent proteolysis of HSF1[38]. Genetic or pharmacological modulation of these targets could be pursued for therapeutic application.

Since most neurodegenerative disorders are typically late-onset, an important question is how aging intersects with protein quality control regulation. TRiC/CCT (chaperonin-containing TCP-1/TCP-1 ring) regulates the folding of ~10% of cytosolic proteins in eukaryotes[39]. Subunits of CCT potently suppress polyglutamine aggregation in an RNA interference screen in *Caenorhabditis elegans*[40], and further studies found that TRiC/CCT counters toxic inclusions of aggregated mutant huntingtin protein (mHtt)[41]. In pluripotent stem cells, assembled TRiC/CCT complexes are abundant, but the levels decline upon differentiation, rendering mature neurons susceptible to mHtt toxicity[42]. Restoring the proteostasis capacity of adult cells by ectopic expression of key subunits that promote TRiC/CCT complex assembly could be an effective neurotherapeutic strategy.

Autophagy–lysosome pathway.

Over the last 15 years, studies of proteostasis dysregulation in neurodegeneration have increasingly focused on the autophagy-lysosome pathway (Fig. 2). Autophagy (macroautophagy) is a catabolic process in which bulk cytosolic contents, protein aggregates, macromolecules, and damaged or excess organelles are packaged into double-membrane-bound vesicles for degradation in lysosomes. The nervous system cannot function normally without proper function of the autophagy pathway[43,44]. In most neurodegenerative disorders, this pathway is dysfunctional, and altered autophagy pathway intermediates accumulate aberrantly[45]. In CAG-polyglutamine repeat diseases, the normal function of the affected proteins has been linked to autophagosome formation (huntingtin) or autophagy pathway activation by transcription factor EB (androgen receptor) or beclin-1 (ataxin-3)[46–48]. Furthermore, mutations in autophagy pathway genes and adaptors result in various neurodegenerative diseases[49,50]. Genes implicated in ALS encode adaptors or regulators of protein degradation[50], whereas genes in PD encode lysosomal proteins or

regulators of endolysosomal trafficking[49]. Endolysosomal trafficking genes have also been implicated in dementia in AD and FTD–ALS[51]. How altered trafficking leads to neuronal demise in these disorders is not fully resolved.

The autophagy–lysosome pathway is also important in metabolic regulation[52]. Given the range of phenotypes arising from different genes in the same pathway, different neurons may express different adaptor proteins or may be more or less reliant on a particular subset of autophagy adaptors. Aberrant trafficking and degradation of pathway function could contribute to the cell-to-cell spread (propagation) of misfolded proteins in the CNS in neurodegenerative disease.

Mitochondrial homeostasis.

Another shared pathway in neurodegeneration is mitochondrial dysfunction (Fig. 2). To function normally, neurons and glia require an abundant and continuous supply of ATP, which is best accomplished by oxidative phosphorylation of glucose. The activities of the mitochondrial respiratory chain complex are impaired in HD, AD, PD, and ALS[53]. Indeed, in PD, exposure to an environmental toxin that blocks mitochondrial complex I can produce Parkinsonism in human patients[54]. Potentially relevant to HD, exposure to 3-nitropropionic acid elicits selective loss of striatal medium spiny neurons in rodents[55]. A selective defect in mitochondrial quality control can also cause PD, as recessive mutations in Parkin or PINK1 cause inherited, early-onset disease, presumably by altering mitochondrial autophagy (mitophagy). In support of mitochondrial dysfunction as a key contributor to HD and sporadic PD, which may be etiologically distinct from toxin exposure, the coactivator PGC-1α and PPAR transcription factors, including PPARδ[56], may be transcriptionally dysregulated in these disorders[57–61].

Cells' capacity to maintain proper mitochondrial quality control through mitophagy and mitochondrial dynamics (fission and fusion) is a recurrent theme in neurodegeneration (Fig. 2). Interestingly, single-gene mutations can produce PD, inherited ataxias, and other neurodegenerative disorders without causing significant nonneural pathology, despite an organism-wide defect in mitochondrial quality control[62]. In Charcot–Marie–Tooth disease type 2A, a peripheral neuropathy caused by haploinsufficiency of mitofusin 2, impaired mitochondrial fusion causes selective degeneration of neurons that require proper shuttling of mitochondria along their lengthy axons[63]. Thus, uninterrupted mitochondrial energy production is essential for normal CNS function. Mitochondrial status has been linked to lysosomal function by showing that mitochondrial oxidative stress precedes lysosomal dysfunction in PD[64] and by identifying a trafficking pathway in which fusion of mitochondria-derived vesicles with late endosomes is regulated by PD-associated proteins[65]. Hence, energy production and proteostasis or mitochondrial quality control are inextricably linked, such that dysfunction of either process will undermine the other in a feedforward fashion.

The efficiency of energy production and of the proteostasis network may decrease with age. Indeed, aging studies reveal decreased autophagy function, possibly from decreased expression of key autophagy genes (for example, *BECN1*) or impaired post-translational regulation, as shown in model organisms[66]. Less robust autophagy would reduce

mitochondrial quality control, owing to less efficient mitophagy of suboptimal mitochondria. Shared mechanisms of reduced autophagy and metabolic function may explain why many neurodegenerative diseases arise in elderly or middle-aged individuals. Further, bioenergetics and proteostasis pathways must be particularly robust in the early years of an organism, as HD and similar inherited diseases can take more than five decades to produce symptoms, despite continuous cellular production of polyglutamine-expanded mHtt. For these reasons, boosting mitochondrial function or enhancing proteostasis might effectively delay the progression of any neurodegenerative disorder, presenting an opportunity to develop a broadly effective therapeutic strategy. Indeed, in worm and mouse models of AD, enhancing mitochondrial proteostasis by genetic or pharmacological means protects against amyloid proteotoxicity[67].

Protein seeding and propagation.

Protein aggregation is common in neurodegeneration and is required for a pathological diagnosis. However, it is unclear whether the culprit is soluble oligomeric species or insoluble fibrillar species, or indeed whether protein aggregation is a protective or neutral event in neuronal cell death. In addition, considerable evidence exists for transcellular propagation and seeding of tau or α-synuclein in in vitro and in vivo models[68–70] (Fig. 2). In sporadic AD, neurofibrillary tangles (NFTs) appear first in the locus coeruleus and entorhinal cortex and then in the hippocampal formation and large parts of the neocortex[71], consistent with propagation across synaptic circuits. Restricting tau expression to entorhinal cortical neurons confirmed that pathological tau spreads from these cells into the hippocampus[72]. In mice expressing wild-type or mutant human tau, intracerebral injection of mutant human tau inclusions induced inclusions that spread to distant brain regions[68]. Similarly, intracerebral injection of brain extracts containing aggregated α-synuclein produced α-synuclein lesions in transgenic or nontransgenic (wild-type) mice[73]. Interestingly, synthetic α-synuclein fibrils induce tauopathy, possibly by a cross-seeding mechanism[74]. Injection of an Aβ-rich brain extract into one brain region triggers deposits in axonally coupled regions that eventually spread to neocortical and subcortical regions[75].

Although cell-to-cell spread of fibrillar pathogenic proteins can be demonstrated experimentally, the role of transmissible spread of pathogens in AD, PD, and FTD is unclear. While the specific characteristics that determine the propagation propensity remain to be determined, a cryo-electron microscopy study to resolve the structure of tau filaments in AD provides insight into the precise regions of the tau that are required for filament formation[76] and may have identified the specific fragment of tau that is needed to seed pathology. This approach could provide structural insights into synuclein and other aggregation-prone disease proteins.

Stress granule biology and protein aggregation.

The aggregation of misfolded proteins in ribonucleoprotein granules—which form in response to environmental toxins, translational inhibition, or other stressors—has been associated with neurodegenerative diseases (Fig. 2). Stress granule core proteins accumulate abnormally in tauopathies[77] and TDP-43 proteinopathies[78], implicating aberrant regulation of stress granule dynamics as a common disease mechanism. Stress granule formation is

regulated by proteins such as T cell-restricted intracellular antigen 1 (TIA-1), RasGAP-associated endoRNase, eukaryotic initiation factor (eIF) 3, and poly-A binding protein[79] and is stimulated by conditions that promote phosphorylation of the initiation factor eIF2α[80]. eIF2α phosphorylation, and thus stress granule formation, is enhanced by oxidative stress (HRI kinase), nutrient limitation or proteasomal dysfunction (GCN2 kinase), viral infection (PKR kinase), and endoplasmic reticulum stress (PERK kinase)[81,82]. Once activated by one of these stresses, RNA-binding proteins rapidly mediate the sequestration of mRNAs encoding nonessential transcripts, while translation of proteins critical for survival and protein quality control persists (for example, molecular chaperones), effectively restructuring the proteome to cope with a challenging environment[79,83]. This highly adaptive mechanism is also dynamic, allowing rapid disassembly of stress granules after resolution of the stress in the nondiseased state[79]. With continual recruitment of RNA-binding proteins through their low-complexity, prion-like protein aggregation domains, stress granules can grow exponentially into liquid-like droplets through a process termed liquid–liquid phase separation[84–86]. Therefore, although stress granules normally protect mRNAs from degradation until the stress is removed, the tendency of resident proteins within stress granules to aggregate suggests that this pathway can be hijacked by other aggregation-prone proteins and contribute to disease pathology.

In tauopathies such as AD and FTD, abundant stress granule pathology often co-localizes with tau pathology[77]. Specifically, stress granule-resident proteins are found in most NFTs, as well as in some inclusions that did not contain pathological tau[77,78]. In cell culture, abnormal tau increases deposition of TIA-1 and accelerates stress granule formation, and reduced TIA-1 expression inhibits the accumulation of pathological tau[87], indicating an intricate relationship between stress granule biology and tau pathophysiology. However, it is unclear whether the deposition of stress granule-resident proteins is simply a consequence of disease or actively regulates disease progression. Crossing PS19 transgenic tau mice with TIA-1-knockout mice revealed that loss of TIA-1 expression reduces stress granule pathology but also enhances both cognitive function and survival in PS19 mice[88]. Unexpectedly, the absence of TIA-1 increased NFT burden and simultaneously reduced levels of soluble, oligomeric tau species. Thus, the aggregation state of tau and the resulting neurotoxicity are inexorably linked to TIA-1. This observation may have important therapeutic implications.

Additional evidence implicating the stress granule pathway in neurodegeneration stems from the discovery of mutations in valosin-containing protein (VCP; also called p97)[89], which is essential for normal stress granule dynamics[90], and in TIA-1 in patients with ALS[91]. Dysfunction of VCP or the autophagy–lysosome system leads to the formation of defective stress granules by allowing incorporation of cellular components that VCP normally targets for lysosomal degradation[92]. These abnormal stress granules may resist disassembly and exacerbate aggregation by cross-seeding with TDP-43. Similarly, ALS-linked mutations in TIA-1 increase aggregation propensity and impede stress granule disassembly, thereby enhancing deposition of stress granules that incorporate TDP-43 and promote its insolubility[91].

Since G_4C_2 hexanucleotide repeat expansions in *C9ORFf72* are the most common genetic cause of ALS and FTD[7,93], it is intriguing that the toxic, arginine-rich (GR and PR) dipeptide repeat proteins generated by repeat-associated non-ATG translation undergo liquid–liquid phase separation and also disrupt the kinetics of stress granule assembly and/or disassembly[94–96]. It will be important to determine how GR and PR dipeptide repeat proteins influence the localization and recruitment of TDP-43 within stress granules. Hence, abnormal stress granule dynamics that favor aggregation and aberrant incorporation of misfolded proteins contribute to the pathophysiology of several neurodegenerative diseases.

Synaptic toxicity and network dysfunction.

Synaptic impairment is a key functional outcome in many neurodegenerative diseases (Fig. 2). Indeed, cognitive impairments in AD are highly correlated with synapse loss in the brain[97]. As shown by positron-emission tomography (PET) imaging, tau aggregates rather than amyloid plaques are closely linked to patterns of neurodegeneration and clinical manifestations of AD[98], consistent with a critical role for tau accumulation in synaptic dysfunction. However, direct evidence that insoluble tau in NFTs is toxic is lacking[99], and much evidence points to soluble tau oligomers as a key toxic species. Reducing levels of soluble tau, including tau oligomers, rescues cognitive deficits without affecting the number of NFTs in tauopathy mouse models[100]. Aberrant post-translational modifications, including acetylation, phosphorylation, and proteolytic cleavage, are implicated in tau-mediated synapse dysfunction. In cultured neurons, tau mutated to mimic the phosphorylation of 14 residues and expressed in neurons reduces the basal number of AMPA receptors (AMPARs) at synapses[101]. Expression of acetyl-mimicking tau causes loss of the postsynaptic scaffold protein KIBRA and impairs AMPAR trafficking during long-term potentiation expression[102]. Tau fragments generated by cleavage of caspase-2 or caspase-3 impair AMPAR-mediated synaptic transmission and induce memory deficits in mice[103], and they disrupt synaptic structure and deplete cell-surface glutamate receptors[104]. Interestingly, synaptic activity induces less toxic forms of mHtt inclusions through a TRiC-dependent mechanism, whereas stimulation of extrasynaptic NMDA receptors results in mtHtt disaggregation, the formation of toxic oligomers, and reduced survival of mtHtt-containing neurons[105].

On the circuit level, synaptic toxicity could result in network instability and promote hypersynchrony, which can lead to network dysfunction. In AD, Aβ-induced synaptic depression affects distinct types of synapses, neurons, and brain regions differently, which could further enhance imbalances and instability[106]. Specifically, GABAergic dysfunction may be key to the pathogenesis of network dysfunction in AD. Deficiency in GABAergic inhibition could arise from impaired inhibitory parvalbumin interneurons, which express lower levels of the voltage-gated sodium channel subunit Nav1.1 in AD brains and in mice expressing humanized APP (hAPP)[107]. Restoring Nav1.1 levels in hAPP mice by Nav1.1–bacterial artificial chromosome (BAC) expression increased inhibitory synaptic activity and reduced hypersynchrony and memory deficits[107]. Remarkably, optogenetically driving fast-spiking, parvalbumin$^+$ interneurons at gamma (40 Hz), but not other frequencies, attenuated AD-associated pathology in mouse models[108]. Thus, network-level interventions could be a new approach to restore cellular health and circuit integrity in neurodegenerative diseases.

Innate immune pathways

The innate immune response protects the host by rapidly detecting and removing pathogens through inflammatory processes[109]. In neurodegenerative diseases, innate immune responses become maladaptive in the form of chronic inflammation, characterized by gliosis and elevated levels of proinflammatory cytokines (Fig. 3). Maladaptive innate immune responses were long considered to be caused by neurodegeneration. However, large-scale human genetic and transcriptomic studies, combined with experimental evidence from animal models, suggest that innate immune mechanisms are a driving force in the pathogenesis of neurodegenerative diseases.

Many genes associated with neurodegenerative diseases regulate innate immune responses. In AD, large-scale GWAS revealed that many risk genes are specifically expressed or enriched in microglia and myeloid cells in the periphery. Whole-genome sequencing studies led to the discovery of rare variants in TREM2 (a transmembrane receptor highly expressed in microglia and myeloid cells) that increase AD risk two-to threefold[110,111]. In a co-expression network analysis, the immune and microglia module—of which TREM2's adaptor TYROBP is a key component—was most relevant for late-onset sporadic AD pathology[23]. C9orf72 hexanucleotide repeat expansion is a common cause of ALS[7]. Highly expressed in myeloid cells, C9orf72 is required for normal immune function. Loss of C9orf72 in mice leads to lysosomal accumulation and altered immune responses in macrophages and microglia, resulting in age-related neuroinflammation similar to that seen in patients with C9orf72 ALS, but not in patients with sporadic ALS[112]. Progranulin (PGRN, *GRN*) haploinsufficiency is a major cause of familialfrontotemporal lobar dementia–TDP[113,114]. PGRN is highly expressed in microglia, and PGRN deficiency in these cells exacerbates proinflammatory responses and microgliosis[115]. Selective removal of PGRN in adult microglia recapitulates some behavioral abnormalities seen in PGRN-deficient mice, such as excessive grooming, supporting a role for microglia dysfunction in PGRN-deficient FTD[116]. Htt is also highly expressed in microglia. In mouse models of HD, expression of mHtt in microglia promotes cell-autonomous proinflammatory transcriptional activation, with an increased capacity to induce neuronal death ex vivo and in vivo[117]. The strong immunomodulatory effects of disease-associated mutations suggest that innate immunity is a factor in neurodegenerative diseases.

Aging and epigenomic changes could also contribute to maladaptive immune responses (Fig. 3). Aging increases basal levels of proinflammatory cytokines and cytokines involved in complement pathway, toll-like receptor signaling, and inflammasome activation, and it reduces levels of anti-inflammatory cytokines[118]. Epigenetic alterations contribute to these changes in innate immune cells. For example, increased expression of TNF-α and IL-1β during aging has been linked to demethylation of its promoter[119,120].

How disease mutations lead to maladaptive immune responses in neurodegenerative disease is largely unknown. An emerging theme is that many disease-linked mutations affect endolysosomal trafficking and protein degradation. Deficiency of C9orf72 or PGRN impairs endolysosomal trafficking and profoundly affects innate immune responses. TREM2-deficient microglia have defective mTOR signaling and abnormal autophagy[121]. TANK-

binding kinase mutations, which cause ALS, are involved in innate immunity signaling pathways and are important in autophagy and mitophagy[122].

As the resident immune cells in the brain, microglia have crucial homeostatic functions, including defense against infection or damage and phagocytosis of debris or dying cells[123]. Microglia also participate in synaptic modulation and provide trophic support for neurons[124]. Adult microglia originate from primitive macrophages[125], and exhibit shared and distinct molecular markers with those of periphery macrophages. Other components of the innate immune response in the brain are perivascular macrophages and astrocytes (Fig. 3). Depending on the injury, astrocytes exhibit distinct activation states and transcriptional signatures[126]. Notably, aberrant microglia signaling can convert astrocytes into neurotoxic reactive astrocytes through release of C1q, TNF, and IL-1α, highlighting the importance of microglia–astrocyte crosstalk in mediating the brain's innate immune responses[126].

One potential mechanism by which maladaptive innate immune responses could drive neurodegeneration is dysfunction in detecting or responding to imbalances in homeostasis, such as accumulation of protein aggregates (Fig. 3). For example, loss of TREM2 inhibits microglia from detecting and clustering around Aβ plaques and damaged neurons, likely by impairing lipid-sensing ability[127]. The disease-associated mutation R47H also impairs detection of lipid ligands by TREM2[127]. Another potential mechanism is impaired ability to phagocytose or clear toxic protein aggregates. Indeed, risk alleles on some genes linked to AD and FTD, such as *CD33* and *GRN*, may contribute to disease by impairing the phagocytosis of Aβ[128,129].

Maladaptive microglia could also damage neuronal circuits through synaptic pruning or cytokine signaling (Fig. 3). AD risk genes such as *APOJ* (clusterin) and complement receptor 1 (*CR1*) are implicated in the classical complement cascade. In mouse models with high Aβ levels, inhibiting C1q, C3, or the microglial complement receptor CR3 reduces the number of phagocytic microglia and early synapse loss[130]. PGRN-knockout mice, a model of PGRN-deficient FTD, have marked microgliosis and preferential elimination of inhibitory synapses in the ventral thalamus[131]. Deleting *C1qa* in these mice reduces synaptic pruning by PGRN-deficient microglia and mitigates neurodegeneration, behavioral phenotypes, and premature mortality[131]. Maladaptive microglia could also regulate neuronal and synaptic activity by cytokines such as TNF-α. Reducing TNF-α levels in PGRN-knockout mice abolishes the hyperexcitability of medium spiny neurons in the nucleus accumbens of the basal ganglia and reduces excessive self-grooming[116]. TNF-α has also been associated with synaptic scaling, a key mechanism of homeostatic plasticity[132]. In a study that used visual deprivation to induce synaptic scaling, the increases in the spine sizes of neurons in the visual cortex were TNF-α-dependent[133]. In PGRN-deficient microglia, the elevated TNF-α levels reflected excessive NF-κB activation, a maladaptive innate response[116].

The alterations in specific circuits induced by maladaptive innate immune responses are puzzling, considering the apparent homogeneity of innate immune cells. For example, microglia enter brain parenchyma at the early embryonic stage with presumably uniform developmental lineage and are similarly distributed across brain regions. However, microglial properties and homeostasis may be greatly shaped by the microenvironment[134].

Even in different subregions of the basal ganglia, microglia differ in transcriptomes and functional properties, such as lysosome content[135]. It is not known whether and how microglial heterogeneity contributes to selective neuronal vulnerabilities in neurodegenerative diseases.

The peripheral immune system can also shape innate immune responses in the brain (Fig. 3). Comprehensive analyses of the human epigenome revealed that late-onset AD variants are more abundant in peripheral immune cells than in resident brain cells[136]. This surprising finding supports a strong involvement of the peripheral innate immune system in AD pathogenesis. In PD patients, proinflammatory microbial metabolites in the gastrointestinal tract have been compellingly linked to microglial activation and α-synuclein aggregation in the brain. Colonization of α-synuclein-overexpressing mice with microbiota from PD patients, but not from healthy controls, enhances physical impairment, supporting a critical contribution from the periphery[137]. Thus, the peripheral immune system could affect brain function independently of pathogenic aggregates, as long observed in the case of sickness behavior and postoperative cognitive decline. The behavioral and cognitive impairments induced by RNA virus depend on brain endothelial and epithelial IFN receptor chain 1 and are mediated by the endothelia-derived chemokine ligand CXCL10[138]. Learning-dependent formation of dendritic spines is impaired by activating the peripheral immune system with poly(I:C), a synthetic analog of double-stranded RNA[139]. Interestingly, inflammation-induced spine alterations require TNF-α and peripheral monocyte-derived cells, but not microglia[139].

Adaptive immunity may also contribute to neurodegenerative disorders. For example, defined peptides derived from cleaved α-synuclein, mutations of which cause PD, act as antigenic epitopes and drive helper and cytotoxic T cell responses in PD patients[140]. Our understanding of how maladaptive peripheral immune responses impair brain function and homeostasis is still in its infancy, but with the advent of novel and more-accessible biomarkers and therapeutic strategies, our knowledge of this process will grow exponentially.

Neurotherapeutics

Insights from disease-gene mapping and molecular cloning have led to detailed cellular and molecular investigations of proteins and pathways implicated in neurodegeneration, and crucial processes of disease pathogenesis have been identified for rare disorders and common diseases. Until recently, however, disease-modifying therapies have remained elusive. We are entering a new era of neuro-degenerative disease research, in which novel therapies to prevent disease or slow its progression could be within our grasp.

One of the most exciting therapeutic strategies envisions the use of a chemical compound or a biological agent to block the production of a disease-causing protein. Various approaches to this dosage-reduction strategy are possible, including viral delivery of short hairpin RNAs to activate the cell's RNA interference machinery. One powerful approach involves antisense oligonucleotides (ASOs), chemically modified single-stranded DNA molecules that bind a target RNA, resulting in digestion by RNAse H or preventing its translation[141,142]. ASOs are

appealing because they can be delivered to the CNS by intrathecal injection using a procedure that is simple and well tolerated. ASOs are being directed against SOD1 in ALS patients and mHtt in HD patients. Indeed, in a Phase 2a clinical trial, an ASO reduced mHtt levels in the CSF in a dose-dependent manner. Enthusiasm for the ASO approach was heightened by US Food and Drug Administration (FDA) approval of the ASO drug nusinersen (Spinraza) to treat autosomal recessive spinal muscular atrophy[143].

Despite their promise as dosage-reducing agents in the brain, ASOs can enter the peripheral circulation and elicit systemic side effects[144]. An alternative strategy is to immunize patients against the toxic disease-causing proteins with an antibody. However, this strategy has not had a beneficial therapeutic effect. The target that has received the greatest amount of attention is $A\beta_{42}$, the peptide that forms the basis for the amyloid cascade hypothesis of AD pathogenesis. Many antibodies have failed in Phase 3 trials in human AD patients, but at least one (aducanumab) showed some promise in an initial small clinical trial[145]. A possible explanation for its potential therapeutic efficacy is its increased affinity for $A\beta_{42}$ fibrils and oligomers and its ability to activate microglia[146]. The development of antibodies to treat neurodegenerative disorders remains an area of intense industry effort and is being extended to intracellular misfolded proteins, which may not be unreasonable if the orderly spreading of toxic proteins from cell to cell turns out to be a required step in the pathogenic cascade.

ASO delivery and passive immunization require periodic lifelong injections, but an ideal therapy would require a single injection. This desire for a ‘one and done’ treatment option, and the growing realization of the power and flexibility of CRISPR-mediated genome editing, has led to therapy development projects that utilize various versions of the CRISPR system[147]. The most appealing diseases for initial genome editing efforts are disorders caused by a single identical mutation; hence, rare inherited neurodegenerative diseases are logical targets for testing CRISPR genome editing approaches. Indeed, ASOs are being piloted as lead therapies for polyglutamine disorders, such as HD. Importantly, current efforts are ‘non-allele selective’, meaning that both the normal huntingtin RNA and the mHtt RNA are being simultaneously targeted for destruction. While there is good reason to believe that such a strategy will not produce side effects, extensive studies in mouse models[148] show that an allele-selective approach would be superior. To that end, one can envision application of CRISPR genome editing to engage only the mutant allele by virtue of SNPs in linkage disequilibrium.

Another exciting application of CRISPR for repeat-expansion diseases is to take advantage of the greater number of guide-RNA binding sites on the mutant expanded repeat allele than on the normal allele and titrate delivery to preferentially target the mutant repeat expansion. This strategy was effective in two recent studies that targeted different sequence motifs in repeat expansion diseases and showed efficacy in a mouse model of myotonic dystrophy[149,150]. Translation of CRISPR-based strategies to patients with neurodegenerative disease will require considerable attention to specificity and elimination of untoward off-target effects before this approach can be advanced to clinical testing. Nevertheless, genome editing has immense neurotherapeutic potential.

In addition to dosage reduction, many other therapeutic approaches are being pursued. As noted above, the decline of robust bioenergetics functions and proteostasis with aging likely contribute to the inability of CNS cells to maintain a compensated state of adequate function in neurodegeneration. Treatment strategies to boost metabolic function and to enhance protein and organelle quality control should hold promise for most neurodegenerative disorders, and efforts to modulate immune function, calcium homeostasis, and synaptic excitotoxicity should also be beneficial in many neurodegenerative diseases. Indeed, while we will continue to pursue one-time definitive interventions as 'blockbuster' therapies for neurodegeneration, combining multiple treatments that individually enhance a distinct fundamental biological CNS process may turn out to be a viable approach to halt disease progression.

References

1. Prince M et al. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement. 9, 63–75.e2 (2013). [PubMed: 23305823]
2. Hurd MD, Martorell P, Delavande A, Mullen KJ & Langa KM Monetary costs of dementia in the United States. N. Engl. J. Med 368, 1326–1334 (2013). [PubMed: 23550670]
3. Taylor JP, Hardy J & Fischbeck KH Toxic proteins in neurodegenerative disease. Science 296, 1991–1995 (2002). [PubMed: 12065827]
4. Goedert M, Eisenberg DS & Crowther RA Propagation of tau aggregates and neurodegeneration. Annu. Rev. Neurosci 40, 189–210 (2017). [PubMed: 28772101]
5. Selkoe DJ & Hardy J The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol. Med 8, 595–608 (2016). [PubMed: 27025652]
6. Hardy J & Orr H The genetics of neurodegenerative diseases. J. Neurochem 97, 1690–1699 10 (2006). [PubMed: 16805777]
7. DeJesus-Hernandez M et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of *C9ORF72* causes chromosome 9p-linked FTD and ALS. Neuron 72, 245–256 (2011). [PubMed: 21944778]
8. Renton AE et al. A hexanucleotide repeat expansion in *C9ORF72* is the cause of chromosome 9p21-linked ALS-FTD. Neuron 72, 257–268 (2011). [PubMed: 21944779]
9. Weishaupt JH, Hyman T & Dikic I Common molecular pathways in amyotrophic lateral sclerosis and frontotemporal dementia. Trends Mol. Med 22, 769–783 (2016). [PubMed: 27498188]
10. Park H, Kim HJ & Jeon BS Parkinsonism in spinocerebellar ataxia. BioMed Res. Int 2015, 125273 (2015). [PubMed: 25866756]
11. Schöls L et al. No Parkinsonism in SCA2 and SCA3 despite severe neurodegeneration of the dopaminergic substantia nigra. Brain 138, 3316–3326 (2015). [PubMed: 26362908]
12. Zimprich A et al. Mutations in LRRK2 cause autosomal-dominant Parkinsonism with pleomorphic pathology. Neuron 44, 601–607 10 (2004). [PubMed: 15541309]
13. Paisán-Ruíz C et al. Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. Neuron 44, 595–600 (2004). [PubMed: 15541308]
14. Chang D et al. A meta-analysis of genome-wide association studies identifies 17 new Parkinson's disease risk loci. Nat. Genet 49, 1511–1516 (2017). [PubMed: 28892059]
15. Scholz SW et al. *SNCA* variants are associated with increased risk for multiple system atrophy. Ann. Neurol 65, 610–614 (2009). [PubMed: 19475667]
16. Bras J et al. Genetic analysis implicates *APOE, SNCA* and suggests lysosomal dysfunction in the etiology of dementia with Lewy bodies. Hum. Mol. Genet 23, 6139–6146 (2014). [PubMed: 24973356]
17. Guerreiro R et al. Investigating the genetic architecture of dementia with Lewy bodies: a two-stage genome-wide association study. Lancet Neurol. 17, 64–74 (2018). [PubMed: 29263008]

18. Huang Y & Mahley RW Apolipoprotein E: structure and function in lipid metabolism, neurobiology, and Alzheimer's diseases. Neurobiol. Dis 72(Pt A), 3–12 (2014). [PubMed: 25173806]
19. Höglinger GU et al. Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. Nat. Genet 43, 699–705 (2011). [PubMed: 21685912]
20. Kouri N et al. Genome-wide association study of corticobasal degeneration identifies risk variants shared with progressive supranuclear palsy. Nat. Commun 6, 7247 (2015). [PubMed: 26077951]
21. Simón-Sánchez J et al. Genome-wide association study reveals genetic risk underlying Parkinson's disease. Nat. Genet 41, 1308–1312 (2009). [PubMed: 19915575]
22. Jones L et al. Genetic evidence implicates the immune system and cholesterol metabolism in the aetiology of Alzheimer's disease. PLoS One 5, e13950 (2010). [PubMed: 21085570]
23. Zhang B et al. Integrated systems approach identifies genetic nodes and networks in late-onset Alzheimer's disease. Cell 153, 707–720 (2013). [PubMed: 23622250]
24. Holmans P et al. A pathway-based analysis provides additional support for an immune-related genetic susceptibility to Parkinson's disease. Hum. Mol. Genet 22, 1039–1049 (2013). [PubMed: 23223016]
25. Moskvina V et al. Analysis of genome-wide association studies of Alzheimer disease and of Parkinson disease to determine if these 2 diseases share a common genetic risk. JAMA Neurol. 70, 1268–1276 (2013). [PubMed: 23921447]
26. Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium. Identification of genetic factors that modify clinical onset of Huntington's disease. Cell 162, 516–526 (2015). [PubMed: 26232222]
27. Jiang B, Glover JN & Weinfeld M Neurological disorders associated with DNA strand-break processing enzymes. Mech. Ageing Dev 161(Pt A), 130–140 (2017). [PubMed: 27470939]
28. Kalia LV et al. Clinical correlations with Lewy body pathology in LRRK2-related Parkinson disease. JAMA Neurol. 72, 100–105 (2015). [PubMed: 25401511]
29. Healy DG et al. Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. Lancet Neurol. 7, 583–590 (2008). [PubMed: 18539534]
30. Sidransky E et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N. Engl. J. Med 361, 1651–1661 (2009). [PubMed: 19846850]
31. Lwin A, Orvisky E, Goker-Alpan O, LaMarca ME & Sidransky E Glucocerebrosidase mutations in subjects with Parkinsonism. Mol. Genet. Metab 81, 70–73 (2004). [PubMed: 14728994]
32. Robak LA et al. Excessive burden of lysosomal storage disorder gene variants in Parkinson's disease. Brain 140, 3191–3203 (2017). [PubMed: 29140481]
33. Boeynaems S, Bogaert E, Van Damme P & Van Den Bosch L Inside out: the role of nucleocytoplasmic transport in ALS and FTLD. Acta Neuropathol. 132, 159–173 (2016). [PubMed: 27271576]
34. Gao FB, Richter JD & Cleveland DW Rethinking unconventional translation in neurodegeneration. Cell 171, 994–1000 (2017). [PubMed: 29149615]
35. Lackie RE et al. The Hsp70/Hsp90 chaperone machinery in neurodegenerative diseases. Front. Neurosci 11, 254 (2017). [PubMed: 28559789]
36. Lindberg I et al. Chaperones in neurodegeneration. J. Neurosci 35, 13853–13859 (2015). [PubMed: 26468185]
37. Shorter J Engineering therapeutic protein disaggregases. Mol. Biol. Cell 27, 1556–1560 (2016). [PubMed: 27255695]
38. Gomez-Pastor R et al. Abnormal degradation of the neuronal stress-protective transcription factor HSF1 in Huntington's disease. Nat. Commun 8, 14405 (2017). [PubMed: 28194040]
39. Spiess C, Meyer AS, Reissmann S & Frydman J Mechanism of the eukaryotic chaperonin: protein folding in the chamber of secrets. Trends Cell Biol. 14, 598–604 5 (2004). [PubMed: 15519848]
40. Nollen EA et al. Genome-wide RNA interference screen identifies previously undescribed regulators of polyglutamine aggregation. Proc. Natl. Acad. Sci. USA 101, 6403–6408 (2004). [PubMed: 15084750]

41. Sontag EM et al. Exogenous delivery of chaperonin subunit fragment ApiCCT1 modulates mutant Huntingtin cellular phenotypes. Proc. Natl. Acad. Sci. USA 110, 3077–3082 (2013). [PubMed: 23365139]
42. Noormohammadi A et al. Somatic increase of CCT8 mimics proteostasis of human pluripotent stem cells and extends *C. elegans* lifespan. Nat. Commun 7, 13649 (2016). [PubMed: 27892468]
43. Hara T et al. Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice. Nature 441, 885–889 (2006). [PubMed: 16625204]
44. Komatsu M et al. Essential role for autophagy protein Atg7 in the maintenance of axonal homeostasis and the prevention of axonal degeneration. Proc. Natl. Acad. Sci. USA 104, 14489–14494 (2007). [PubMed: 17726112]
45. Menzies FM et al. Autophagy and neurodegeneration: pathogenic mechanisms and therapeutic opportunities. Neuron 93, 1015–1034 (2017). [PubMed: 28279350]
46. Ashkenazi A et al. Polyglutamine tracts regulate beclin 1-dependent autophagy. Nature 545, 108–111 (2017). [PubMed: 28445460]
47. Cortes CJ et al. Polyglutamine-expanded androgen receptor interferes with TFEB to elicit autophagy defects in SBMA. Nat. Neurosci 17, 1180–1189 (2014). [PubMed: 25108912]
48. Ochaba J et al. Potential function for the Huntingtin protein as a scaffold for selective autophagy. Proc. Natl. Acad. Sci. USA 111, 16889–16894 (2014). [PubMed: 25385587]
49. Abeliovich A & Gitler AD Defects in trafficking bridge Parkinson's disease pathology and genetics. Nature 539, 207–216 (2016). [PubMed: 27830778]
50. Taylor JP, Brown RH, Jr. & Cleveland DW Decoding ALS: from genes to mechanism. Nature 539, 197–206 (2016). [PubMed: 27830784]
51. Wang C, Telpoukhovskaia MA, Bahr BA, Chen X & Gan L Endo-lysosomal dysfunction: a converging mechanism in neurodegenerative diseases. Curr. Opin. Neurobiol 48, 52–58 (2018). [PubMed: 29028540]
52. Settembre C, Fraldi A, Medina DL & Ballabio A Signals from the lysosome: a control centre for cellular clearance and energy metabolism. Nat. Rev. Mol. Cell Biol 14, 283–296 (2013). [PubMed: 23609508]
53. Golpich M et al. Mitochondrial dysfunction and biogenesis in neurodegenerative diseases: pathogenesis and treatment. CNS Neurosci. Ther 23, 5–22 (2017). [PubMed: 27873462]
54. Dauer W & Przedborski S Parkinson's disease: mechanisms and models. Neuron 39, 889–909 (2003). [PubMed: 12971891]
55. Beal MF et al. Neurochemical and histologic characterization of striatal excitotoxic lesions produced by the mitochondrial toxin 3-nitropropionic acid. J. Neurosci 13, 4181–4192 (1993). [PubMed: 7692009]
56. Dickey AS et al. PPAR-δ is repressed in Huntington's disease, is required for normal neuronal function and can be targeted therapeutically. Nat. Med 22, 37–45 (2016). [PubMed: 26642438]
57. Chaturvedi RK et al. Impaired PGC-1alpha function in muscle in Huntington's disease. Hum. Mol. Genet 18, 3048–3065 (2009). [PubMed: 19460884]
58. Cui L et al. Transcriptional repression of PGC-1alpha by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration. Cell 127, 59–69 (2006). [PubMed: 17018277]
59. Shin JH et al. PARIS (ZNF746) repression of PGC-1a contributes to neurodegeneration in Parkinson's disease. Cell 144, 689–702 (2011). [PubMed: 21376232]
60. Weydt P et al. Thermoregulatory and metabolic defects in Huntington's disease transgenic mice implicate PGC-1alpha in Huntington's disease neurodegeneration. Cell Metab. 4, 349–362 (2006). [PubMed: 17055784]
61. Zheng B et al. PGC-1α, a potential therapeutic target for early intervention in Parkinson's disease. Sci. Transl. Med 2, 52ra73 (2010).
62. Batlevi Y & La Spada AR Mitochondrial autophagy in neural function, neurodegenerative disease, neuron cell death, and aging. Neurobiol. Dis 43, 46–51 (2011). [PubMed: 20887789]
63. Burte F, Carelli V, Chinnery PF & Yu-Wai-Man P Disturbed mitochondrial dynamics and neurodegenerative disorders. Nat. Rev. Neurol 11, 11–24 (2015). [PubMed: 25486875]

64. Burbulla LF et al. Dopamine oxidation mediates mitochondrial and lysosomal dysfunction in Parkinson's disease. Science 357, 1255–1261 (2017). [PubMed: 28882997]
65. Sugiura A, McLelland GL, Fon EA & McBride HM A new pathway for mitochondrial quality control: mitochondrial-derived vesicles. EMBO J. 33, 2142–2156 (2014). [PubMed: 25107473]
66. Cuervo AM Autophagy and aging: keeping that old broom working. Trends Genet. 24, 604–612 (2008). [PubMed: 18992957]
67. Sorrentino V et al. Enhancing mitochondrial proteostasis reduces amyloid-β proteotoxicity. Nature 552, 187–193 (2017). [PubMed: 29211722]
68. Clavaguera F et al. Transmission and spreading of tauopathy in transgenic mouse brain. Nat. Cell Biol 11, 909–913 (2009). [PubMed: 19503072]
69. Frost B, Ollesch J, Wille H & Diamond MI Conformational diversity of wild-type Tau fibrils specified by templated conformation change. J. Biol. Chem 284, 3546–3551 (2009). [PubMed: 19010781]
70. Guo JL & Lee VM Seeding of normal Tau by pathological Tau conformers drives pathogenesis of Alzheimer-like tangles. J. Biol. Chem 286, 15317–15331 (2011). [PubMed: 21372138]
71. Braak H & Braak E Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 82, 239–259 (1991). [PubMed: 1759558]
72. de Calignon A et al. Propagation of tau pathology in a model of early Alzheimer's disease. Neuron 73, 685–697 (2012). [PubMed: 22365544]
73. Luk KC et al. Pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. Science 338, 949–953 (2012). [PubMed: 23161999]
74. Guo JL et al. Distinct α-synuclein strains differentially promote tau inclusions in neurons. Cell 154, 103–117 (2013). [PubMed: 23827677]
75. Jucker M & Walker LC Self-propagation of pathogenic protein aggregates in neurodegenerative diseases. Nature 501, 45–51 (2013). [PubMed: 24005412]
76. Fitzpatrick AWP et al. Cryo-EM structures of tau filaments from Alzheimer's disease. Nature 547, 185–190 (2017). [PubMed: 28678775]
77. Vanderweyde T et al. Contrasting pathology of the stress granule proteins TIA-1 and G3BP in tauopathies. J. Neurosci 32, 8270–8283 (2012). [PubMed: 22699908]
78. Liu-Yesucevitz L et al. Tar DNA binding protein-43 (TDP-43) associates with stress granules: analysis of cultured cells and pathological brain tissue. PLoS One 5, e13250 (2010). [PubMed: 20948999]
79. Anderson P & Kedersha N Stress granules: the Tao of RNA triage. Trends Biochem. Sci 33, 141–150 (2008). [PubMed: 18291657]
80. Kedersha NL, Gupta M, Li W, Miller I & Anderson P RNA-binding proteins TIA-1 and TIAR link the phosphorylation of eIF-2 alpha to the assembly of mammalian stress granules. J. Cell Biol 147, 1431–1442 (1999). [PubMed: 10613902]
81. Boyce M et al. A selective inhibitor of eIF2alpha dephosphorylation protects cells from ER stress. Science 307, 935–939 (2005). [PubMed: 15705855]
82. Mazroui R, Di Marco S, Kaufman RJ & Gallouzi IE Inhibition of the ubiquitin-proteasome system induces stress granule formation. Mol. Biol. Cell 18, 2603–2618 (2007). [PubMed: 17475769]
83. Kawai T, Fan J, Mazan-Mamczarz K & Gorospe M Global mRNA stabilization preferentially linked to translational repression during the endoplasmic reticulum stress response. Mol. Cell. Biol 24, 6773–6787 (2004). [PubMed: 15254244]
84. Gopal PP, Nirschl JJ, Klinman E & Holzbaur EL Amyotrophic lateral sclerosis-linked mutations increase the viscosity of liquid-like TDP-43 RNP granules in neurons. Proc. Natl. Acad. Sci. USA 114, E2466–E2475 (2017). [PubMed: 28265061]
85. Patel A et al. A liquid-to-solid phase transition of the ALS protein FUS accelerated by disease mutation. Cell 162, 1066–1077 (2015). [PubMed: 26317470]
86. Molliex A et al. Phase separation by low complexity domains promotes stress granule assembly and drives pathological fibrillization. Cell 163, 123–133 (2015). [PubMed: 26406374]
87. Vanderweyde T et al. Interaction of tau with the RNA-binding protein TIA1 regulates tau pathophysiology and toxicity. Cell Rep. 15, 1455–1466 (2016). [PubMed: 27160897]

88. Apicco DJ et al. Reducing the RNA binding protein TIA1 protects against tau-mediated neurodegeneration in vivo. Nat. Neurosci 21, 72–80 (2018). [PubMed: 29273772]
89. Johnson JO et al. Exome sequencing reveals VCP mutations as a cause of familial ALS. Neuron 68, 857–864 (2010). [PubMed: 21145000]
90. Buchan JR, Kolaitis RM, Taylor JP & Parker R Eukaryotic stress granules are cleared by autophagy and Cdc48/VCP function. Cell 153, 1461–1474 (2013). [PubMed: 23791177]
91. Mackenzie IR et al. TIA1 mutations in amyotrophic lateral sclerosis and frontotemporal dementia promote phase separation and alter stress granule dynamics. Neuron 95, 808–816.e9 (2017). [PubMed: 28817800]
92. Seguin SJ et al. Inhibition of autophagy, lysosome and VCP function impairs stress granule assembly. Cell Death Differ. 21, 1838–1851 (2014). [PubMed: 25034784]
93. Cirulli ET et al. Exome sequencing in amyotrophic lateral sclerosis identifies risk genes and pathways. Science 347, 1436–1441 (2015). [PubMed: 25700176]
94. Lee KH et al. C9orf72 dipeptide repeats impair the assembly, dynamics, and function of membrane-less organelles. Cell 167, 774–788.e17 (2016). [PubMed: 27768896]
95. Lin Y et al. Toxic PR poly-dipeptides encoded by the C9orf72 repeat expansion target LC domain polymers. Cell 167, 789–802.e12 (2016). [PubMed: 27768897]
96. Boeynaems S et al. Phase separation of C9orf72 dipeptide repeats perturbs stress granule dynamics. Mol. Cell 65, 1044–1055.e5 (2017). [PubMed: 28306503]
97. Masliah E, Hansen L, Albright T, Mallory M & Terry RD Immunoelectron microscopic study of synaptic pathology in Alzheimer's disease. Acta Neuropathol. 81, 428–433 (1991). [PubMed: 1903014]
98. Ossenkoppele R et al. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. Brain 139, 1551–1567 (2016). [PubMed: 26962052]
99. Spires-Jones TL & Hyman BT The intersection of amyloid beta and tau at synapses in Alzheimer's disease. Neuron 82, 756–771 (2014). [PubMed: 24853936]
100. Santacruz K et al. Tau suppression in a neurodegenerative mouse model improves memory function. Science 309, 476–481 (2005). [PubMed: 16020737]
101. Hoover BR et al. Tau mislocalization to dendritic spines mediates synaptic dysfunction independently of neurodegeneration. Neuron 68, 1067–1081 (2010). [PubMed: 21172610]
102. Tracy TE et al. Acetylated tau obstructs KIBRA-mediated signaling in synaptic plasticity and promotes tauopathy-related memory loss. Neuron 90, 245–260 (2016). [PubMed: 27041503]
103. Zhao X et al. Caspase-2 cleavage of tau reversibly impairs memory. Nat. Med 22, 1268–1276 (2016). [PubMed: 27723722]
104. Zhao Y et al. Appoptosin-mediated caspase cleavage of tau contributes to progressive supranuclear palsy pathogenesis. Neuron 87, 963–975 (2015). [PubMed: 26335643]
105. Okamoto S et al. Balance between synaptic versus extrasynaptic NMDA receptor activity influences inclusions and neurotoxicity of mutant huntingtin. Nat. Med 15, 1407–1413 (2009). [PubMed: 19915593]
106. Palop JJ & Mucke L Network abnormalities and interneuron dysfunction in Alzheimer disease. Nat. Rev. Neurosci 17, 777–792 (2016). [PubMed: 27829687]
107. Verret L et al. Inhibitory interneuron deficit links altered network activity and cognitive dysfunction in Alzheimer model. Cell 149, 708–721 (2012). [PubMed: 22541439]
108. Iaccarino HF et al. Gamma frequency entrainment attenuates amyloid load and modifies microglia. Nature 540, 230–235 (2016). [PubMed: 27929004]
109. Medzhitov R Origin and physiological roles of inflammation. Nature 454, 428–435 (2008). [PubMed: 18650913]
110. Jonsson T et al. Variant of TREM2 associated with the risk of Alzheimer's disease. N. Engl. J. Med 368, 107–116 (2013). [PubMed: 23150908]
111. Guerreiro R et al. TREM2 variants in Alzheimer's disease. N. Engl. J. Med 368, 117–127 (2013). [PubMed: 23150934]
112. O'Rourke JG et al. C9orf72 is required for proper macrophage and microglial function in mice. Science 351, 1324–1329 (2016). [PubMed: 26989253]

113. Baker M et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature 442, 916–919 (2006). [PubMed: 16862116]
114. Cruts M, Kumar-Singh S & Van Broeckhoven C Progranulin mutations in ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Curr. Alzheimer Res 3, 485–491 (2006). [PubMed: 17168647]
115. Yin F et al. Exaggerated inflammation, impaired host defense, and neuropathology in progranulin-deficient mice. J. Exp. Med 207, 117–128 (2010). [PubMed: 20026663]
116. Krabbe G et al. Microglial NFκB-TNFα hyperactivation induces obsessive-compulsive behavior in mouse models of progranulin-deficient frontotemporal dementia. Proc. Natl. Acad. Sci. USA 114, 5029–5034 (2017). [PubMed: 28438992]
117. Crotti A et al. Mutant Huntingtin promotes autonomous microglia activation via myeloid lineage-determining factors. Nat. Neurosci 17, 513–521 (2014). [PubMed: 24584051]
118. Cribbs DH et al. Extensive innate immune gene activation accompanies brain aging, increasing vulnerability to cognitive decline and neurodegeneration: a microarray study. J. Neuroinflammation 9, 179 (2012). [PubMed: 22824372]
119. Gowers IR et al. Age-related loss of CpG methylation in the tumour necrosis factor promoter. Cytokine 56, 792–797 (2011). [PubMed: 22004920]
120. Cho SH et al. SIRT1 deficiency in microglia contributes to cognitive decline in aging and neurodegeneration via epigenetic regulation of IL-1 β. J. Neurosci 35, 807–818 (2015). [PubMed: 25589773]
121. Ulrich JD, Ulland TK, Colonna M & Holtzman DM Elucidating the role of TREM2 in Alzheimer's disease. Neuron 94, 237–248 (2017). [PubMed: 28426958]
122. Oakes JA, Davies MC & Collins MO TBK1: a new player in ALS linking autophagy and neuroinflammation. Mol. Brain 10, 5 (2017). [PubMed: 28148298]
123. Salter MW & Stevens B Microglia emerge as central players in brain disease. Nat. Med 23, 1018–1027 (2017). [PubMed: 28886007]
124. Parkhurst CN et al. Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. Cell 155, 1596–1609 (2013). [PubMed: 24360280]
125. Ginhoux F et al. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. Science 330, 841–845 (2010). [PubMed: 20966214]
126. Liddelow SA et al. Neurotoxic reactive astrocytes are induced by activated microglia. Nature 541, 481–487 (2017). [PubMed: 28099414]
127. Wang Y et al. TREM2 lipid sensing sustains the microglial response in an Alzheimer's disease model. Cell 160, 1061–1071 (2015). [PubMed: 25728668]
128. Griciuc A et al. Alzheimer's disease risk gene CD33 inhibits microglial uptake of amyloid beta. Neuron 78, 631–643 (2013). [PubMed: 23623698]
129. Minami SS et al. Progranulin protects against amyloid β deposition and toxicity in Alzheimer's disease mouse models. Nat. Med 20, 1157–1164 (2014). [PubMed: 25261995]
130. Hong S et al. Complement and microglia mediate early synapse loss in Alzheimer mouse models. Science 352, 712–716 (2016). [PubMed: 27033548]
131. Lui H et al. Progranulin deficiency promotes circuit-specific synaptic pruning by microglia via complement activation. Cell 165, 921–935 (2016). [PubMed: 27114033]
132. Stellwagen D & Malenka RC Synaptic scaling mediated by glial TNF-alpha. Nature 440, 1054–1059 (2006). [PubMed: 16547515]
133. Barnes SJ et al. Deprivation-induced homeostatic spine scaling in vivo is localized to dendritic branches that have undergone recent spine loss. Neuron 96, 871–882.e5 (2017). [PubMed: 29107520]
134. Gosselin D et al. An environment-dependent transcriptional network specifies human microglia identity. Science 356, eaal3222 (2017). [PubMed: 28546318]
135. De Biase LM et al. Local cues establish and maintain region-specific phenotypes of basal ganglia microglia. Neuron 95, 341–356.e6 (2017). [PubMed: 28689984]
136. Kundaje A et al. Integrative analysis of 111 reference human epigenomes. Nature 518, 317–330 (2015). [PubMed: 25693563]

137. Sampson TR et al. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. Cell 167, 1469–1480.e12 (2016). [PubMed: 27912057]

138. Blank T et al. Brain endothelial-and epithelial-specific Interferon Receptor Chain 1 drives virus-induced sickness behavior and cognitive impairment. Immunity 44, 901–912 (2016). [PubMed: 27096319]

139. Garré JM, Silva HM, Lafaille JJ & Yang G $CX3CR1^{+}$ monocytes modulate learning and learning-dependent dendritic spine remodeling via TNF-α. Nat. Med 23, 714–722 (2017). [PubMed: 28504723]

140. Sulzer D et al. T cells from patients with Parkinson's disease recognize α-synuclein peptides. Nature 546, 656–661 (2017). [PubMed: 28636593]

141. Martínez T, Wright N, López-Fraga M, Jiménez AI & Pañeda C Silencing human genetic diseases with oligonucleotide-based therapies. Hum. Genet 132, 481–493 (2013). [PubMed: 23494242]

142. Lu XH & Yang XW "Huntingtin holiday": progress toward an antisense therapy for Huntington's disease. Neuron 74, 964–966 (2012). [PubMed: 22726826]

143. Finkel RS et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N. Engl. J. Med 377, 1723–1732 (2017). [PubMed: 29091570]

144. Mustonen EK, Palomäki T & Pasanen M Oligonucleotide-based pharmaceuticals: non-clinical and clinical safety signals and non-clinical testing strategies. Regul. Toxicol. Pharmacol 90, 328–341 (2017). [PubMed: 28966105]

145. Sevigny J et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature 537, 50–56 (2016). [PubMed: 27582220]

146. Reiman EM Alzheimer's disease: attack on amyloid-β protein. Nature 537, 36–37 (2016). [PubMed: 27582214]

147. Wright AV, Nuñez JK & Doudna JA Biology and applications of CRISPR systems: harnessing nature's toolbox for genome engineering. Cell 164, 29–44 (2016). [PubMed: 26771484]

148. Kordasiewicz HB et al. Sustained therapeutic reversal of Huntington's disease by transient repression of huntingtin synthesis. Neuron 74, 1031–1044 (2012). [PubMed: 22726834]

149. Batra R et al. Elimination of toxic microsatellite repeat expansion RNA by RNA-targeting Cas9. Cell 170, 899–912.e10 (2017). [PubMed: 28803727]

150. Pinto BS et al. Impeding transcription of expanded microsatellite repeats by deactivated Cas9. Mol. Cell 68, 479–490.e5 (2017). [PubMed: 29056323]

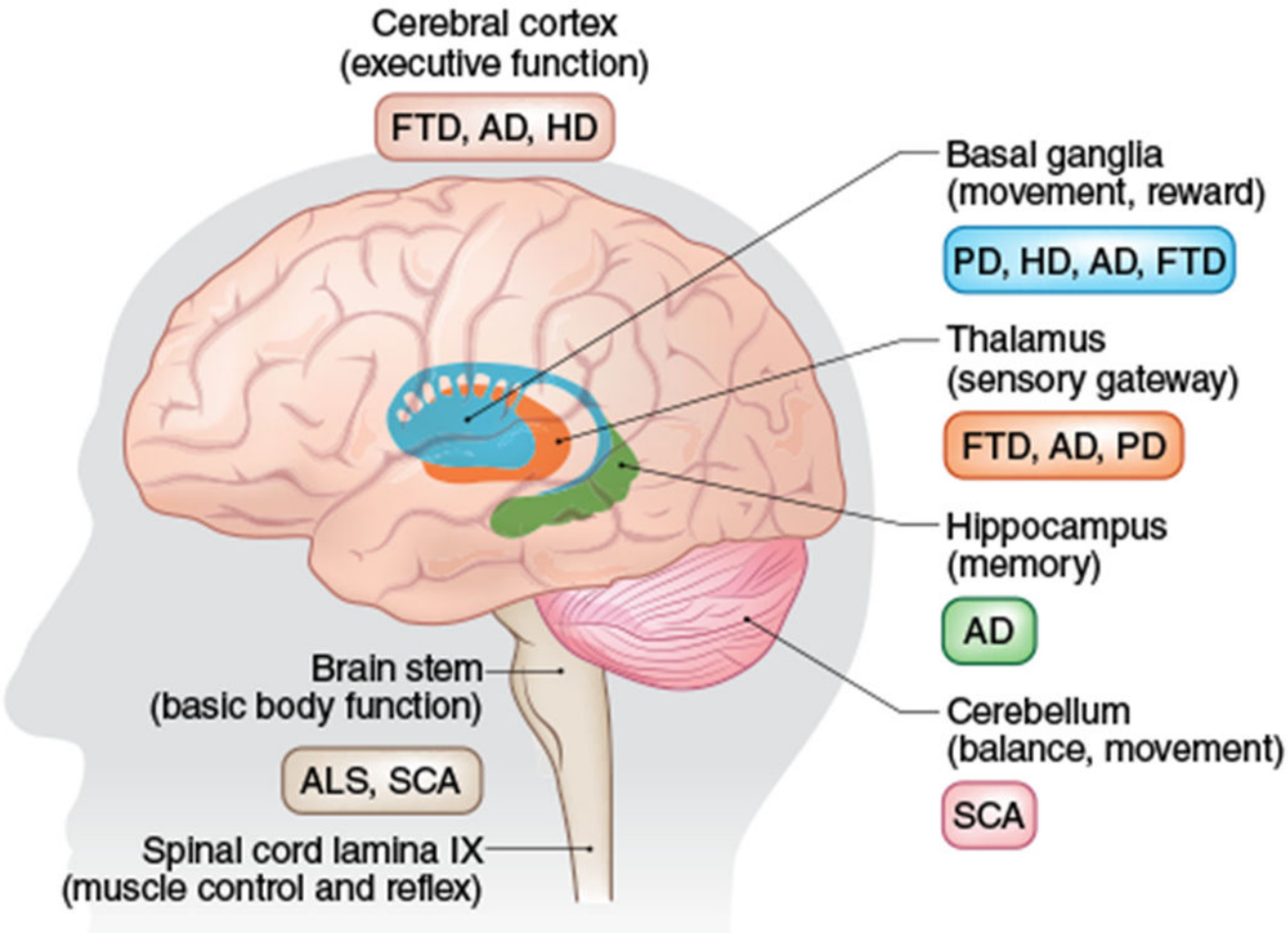

Fig. 1|. Primary brain regions affected in major neurodegenerative diseases.

Clinical manifestations reflect distinct and overlapping neuronal circuits that progressively degenerate in various neurodegenerative diseases.

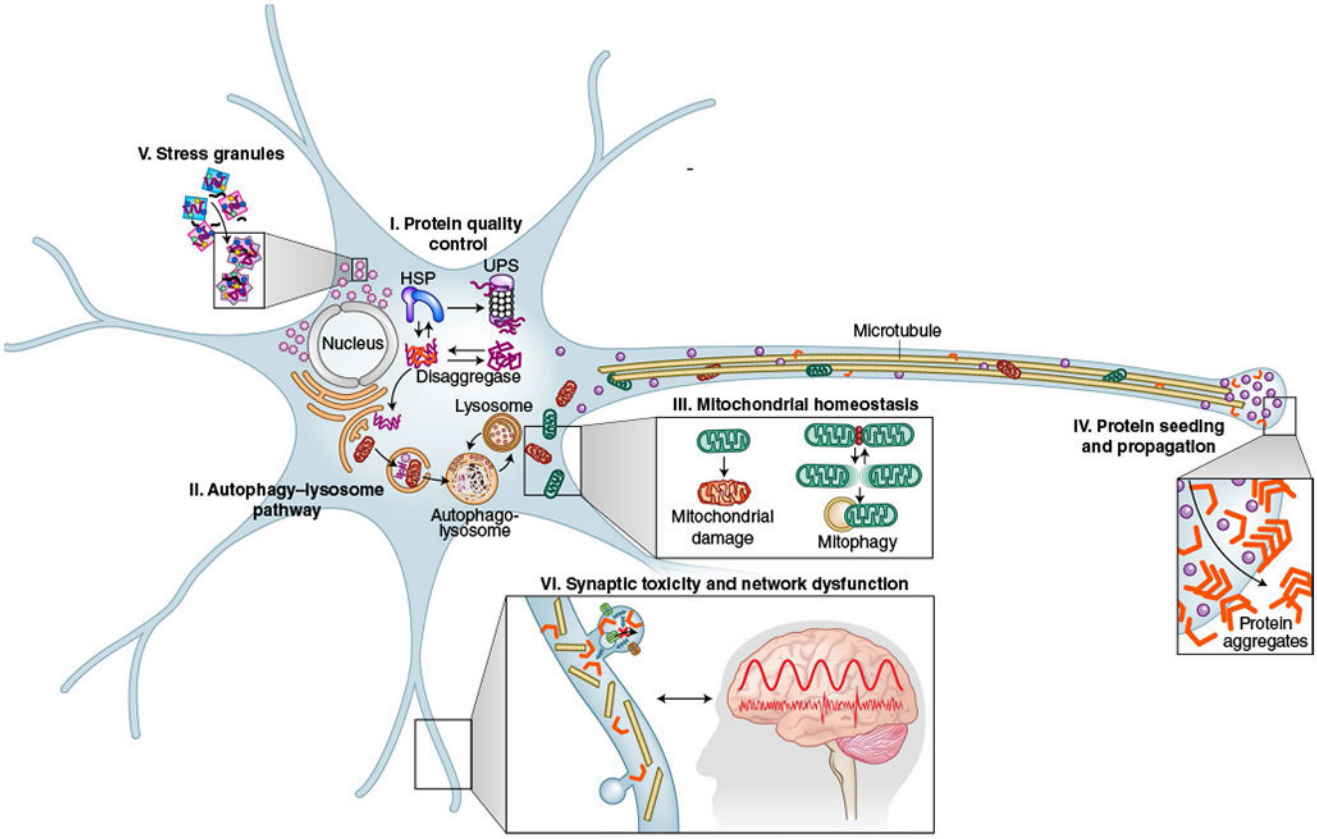

Fig. 2|. Common neuronal pathways altered in multiple neurodegenerative diseases, including protein quality control, the autophagy-lysosome pathway, mitochondria homeostasis, protein seeding and propagation of stress granules, and synaptic toxicity and network dysfunction.

Inset I: molecular chaperones, including HSP, regulate protein folding and ubiquitin-proteasome system (UPS)-mediated degradation, while disaggregase could return misfolded proteins to their natively folded and functional state. Inset II: dysfunction in the autophagy-lysosomal pathway could underlie accumulation of pathogenic protein aggregates and damaged mitochondria. Inset III: impairment of mitochondrial quality control through mitophagy and mitochondrial dynamics results in reduced energy production and dysfunctional proteostasis network. Inset IV: transcellular propagation and seeding of protein aggregates could underlie the disease progression. Inset V: abnormal stress granule dynamics that favor aggregation and aberrant incorporation of misfolded proteins contributes to toxicity. Inset VI: soluble forms of protein assemblies induce both pre- and postsynaptic impairments, leading to network dysfunction. HSP; heat shock protein.

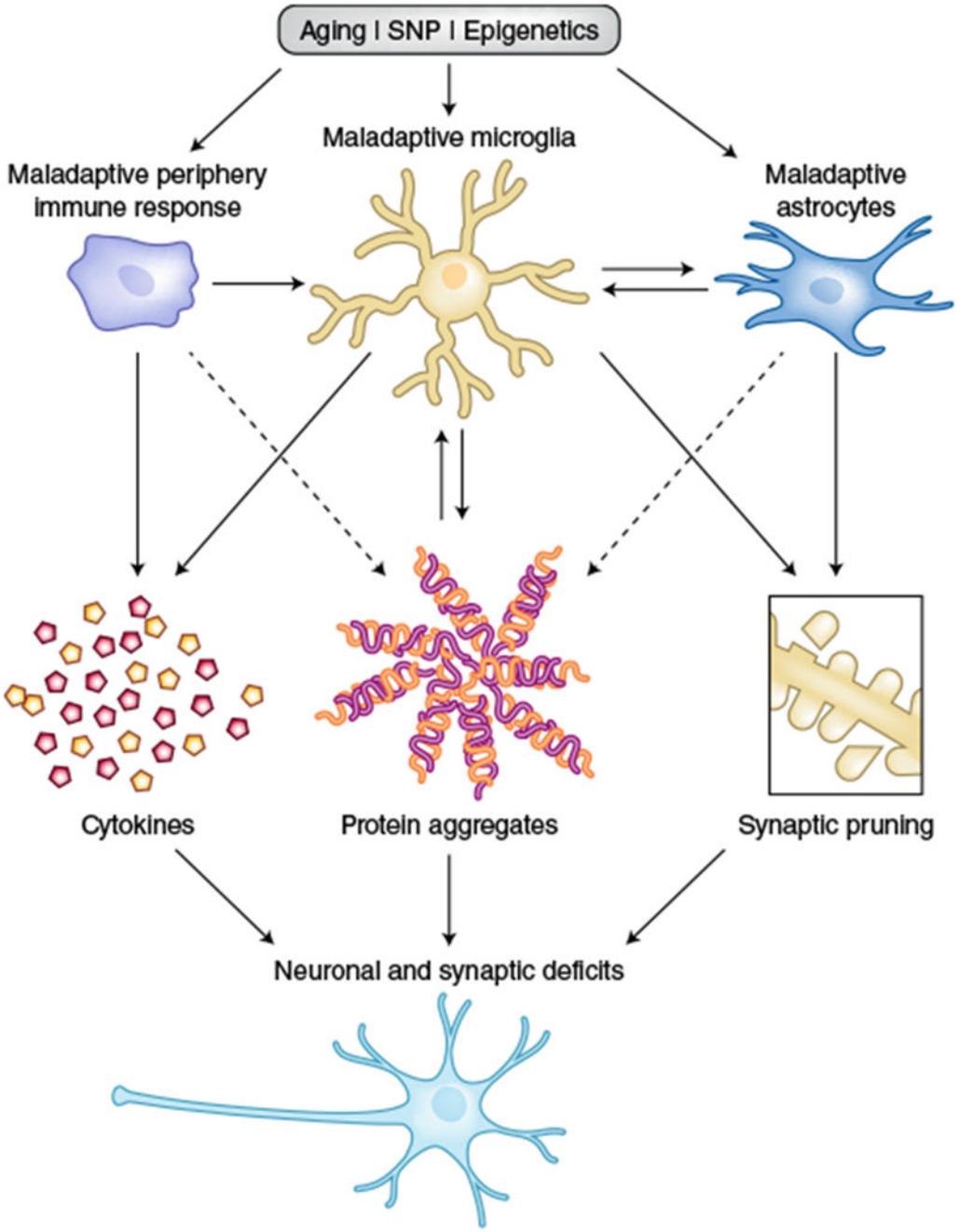

Fig. 3|. Innate immune pathways in neurodegenerative diseases.

A maladaptive innate immune response has emerged as a critical driving force in the pathogenesis of many neurodegenerative diseases. SNPs on many disease-associate genes induce maladaptive innate immune responses that are also associated with aging and epigenetic changes. Microglia, the resident immune cells in the brain, engage in crosstalk with astroglia and are modulated by peripheral immune system. Maladaptive microglia could damage neuronal circuits due to dysfunction in their detection or response to homeostasis imbalance, resulting in accumulation of protein aggregates, in concert with

astroglia and possibly the peripheral immune system. Microglia could also cause neuronal and network dysfunction by altering cytokine signaling and synaptic pruning, independently of their effects on protein aggregates.