

Basic mechanisms of neurodegeneration: a critical update

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Abstract

Neurodegenerative diseases are characterized by progressive dysfunction of specific populations of neurons, determining clinical presentation. Neuronal loss is associated with extra and intracellular accumulation of misfolded proteins, the hallmarks of many neurodegenerative *proteinopathies*. Major basic processes include abnormal protein dynamics due to deficiency of the ubiquitin–proteasome–autophagy system, oxidative stress and free radical formation, mitochondrial dysfunction, impaired bioenergetics, dysfunction of neurotrophins, 'neuroinflammatory' processes and (secondary) disruptions of neuronal Golgi apparatus and axonal transport. These interrelated mechanisms lead to programmed cell death is a long run over many years. Neurodegenerative disorders are classified according to known genetic mechanisms or to major components of protein deposits, but recent studies showed both overlap and intraindividual diversities between different phenotypes. Synergistic mechanisms between pathological proteins suggest common pathogenic mechanisms. Animal models and other studies have provided insight into the basic neurodegeneration and cell death programs, offering new ways for future prevention/treatment strategies.

Keywords: neurodegeneration • proteinopathies • pathogenic factors • oxidative stress • bioenergetic deficiency • mitochondrial defects • neuronal dysfunction/death

Introduction

Neurodegenerative disorders (NDD) constitute a set of pathological conditions originating from slow progressive and irreversible dysfunction and loss of neurons and synapses in selected areas of the nervous system which determine clinical presentation and course. The major basic mechanisms leading to neurodegeneration (ND) are considered multifactorial caused by genetic, environmental and endogenous factors related to aging, but their pathogenic role and their basic molecular mechanisms are not fully

understood [1, 2]. NDDs currently are classified according to known genetic mechanisms and/or to the major compounds of their protein deposits (Fig. 1). Based on critical conformational changes of proteins, these disorders are denoted as 'protein misfolding' diseases or proteinopathies [3, 4]. Recent progress with respect to the triggers of most NDDs is illustrated by the number of citations in PubMed (December 4, 2009): ND 37,019; NDDs 168,827; pathogenesis 89,008.

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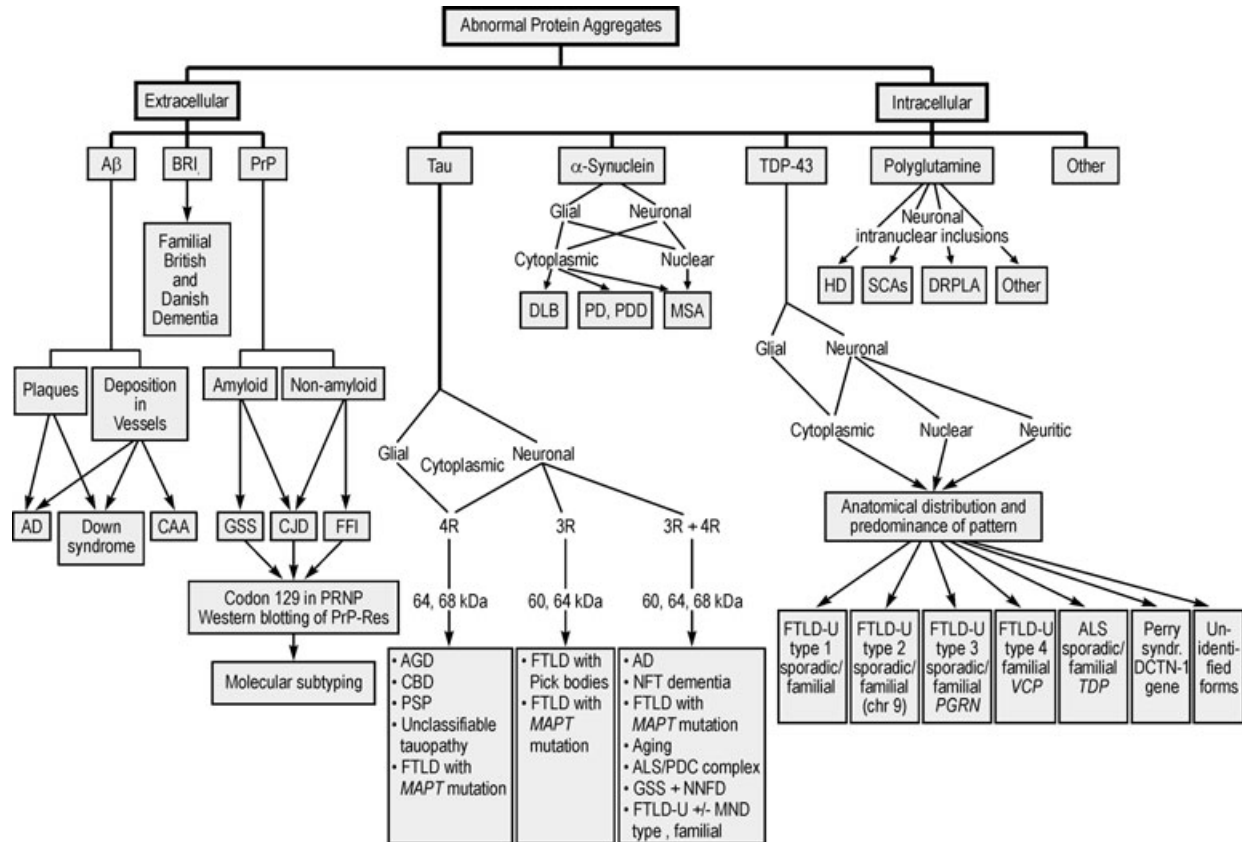


Fig. 1 Algorithm for classification of neurodegenerative diseases with protein deposits (proteinopathies) (from [1]).

- Common pathogenic mechanisms underlying many NDDs include:
1. Abnormal protein dynamics with misfolding, defective degradation, proteasomal dysfunction and aggregation; often with actions and mutations of molecular chaperones;
 2. Oxidative stress (OS) and formation of free radicals/reactive oxygen species (ROS);
 3. Impaired bioenergetics, mitochondrial dysfunctions and DNA damage;
 4. Fragmentation of neuronal Golgi apparatus;
 5. Disruption of cellular/axonal transport (4 and 5 may be regarded as secondary effects);
 6. Dysfunction of neurotrophins (NTFs) and
 7. 'Neuroinflammatory'/neuroimmune processes.

These mechanisms are interrelated in complex vicious circles finally leading to cell dysfunction and death, the basic molecular cascades of which under discussion.

Protein aggregation

Abnormal interactions between proteins that result in aberrant intra and extracellular deposition of self-aggregating misfolded

proteins with formation of high-ordered insoluble fibrils are pathological hallmarks of many, albeit diverse, NDDs [see 1, 2, 5, 6]. In general, the identity of the underlying protein determines which neurons are affected and, hence, the clinical manifestation of each disease [7, 8]. However, the same neuronal populations can be affected by different disorders. The same neurodegenerative process and the same mutation in the genes encoding protein constituents may be associated with a variety of clinico-pathological phenotypes, whereas similar or identical phenotypes may be related to different genetic defects, resulting from complex gene-gene and gene-environmental interplay [9]. Abnormal protein-protein interactions and/or the lesions that result from them trigger vicious circles leading to dysfunction and death of neuronal and glial cells with ensuing disintegration of neuronal networks [10, 11]. Abnormal interaction between normal, highly soluble brain proteins alters their conformation, and misfolding gradually converts them into insoluble polymers with the aggregates adopting either highly ordered (cross-pleated β -sheet structures) or disordered (amorphous) forms [12]. Since deposits of natively unfolded proteins aggregated into defined fibrillar structures often display the properties of amyloid (*i.e.* ~10-nm-wide fibrils with crossed β -pleated sheet structures), these disorders are grouped together as brain amyloidoses [2, 13].

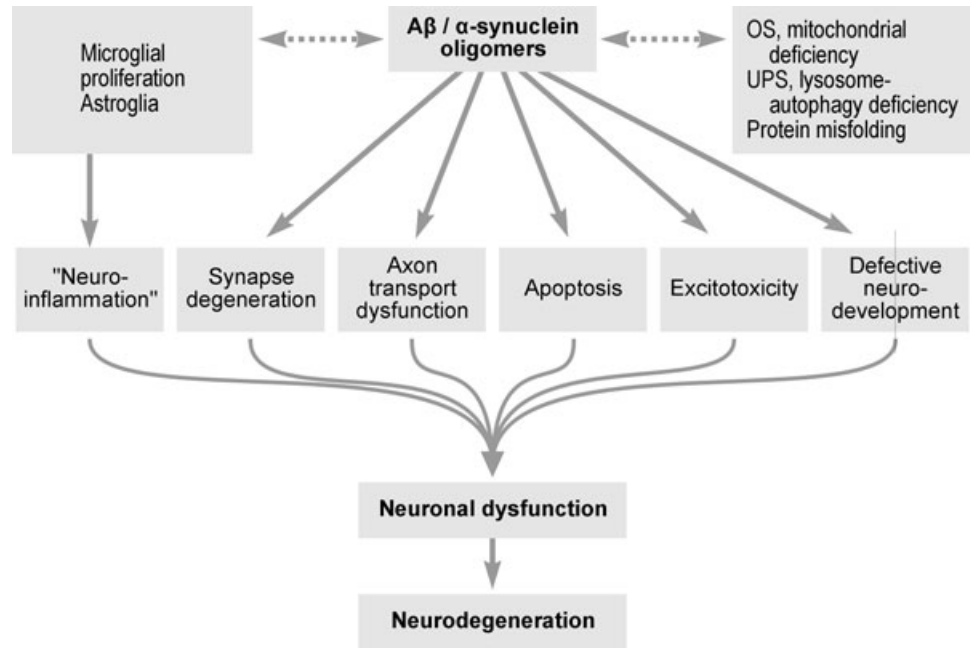


Fig. 2 Cascade of neurotoxic effects of protein oligomers leading to neuronal dysfunction/ND; illustrated by the suggested relationship between A β and α Syn oligomers.

'Toxic oligomer' hypothesis

A causative link between the formation of protein aggregates and ND is suggested to be a result of the toxic action of substances produced during early phases, *i.e.* soluble oligomers and protofibrillar derivatives of misfolded proteins [14–16]. However, the precise biochemical mechanisms are poorly understood.

The 'toxic oligomer' hypothesis is supported by the finding that a single-domain antibody can recognize a common conformational epitope that is displayed by several disease-associated proteins, including β -amyloid (A β), α -synuclein (α Syn), τ protein, prions and polyglutamine (polyQ) peptides [17–20] (Fig. 2). Soluble A β oligomers are increased in Alzheimer's disease (AD) in both brain tissue and plasma [21], and their levels correlate with cognitive dysfunction [22]. The analysis of the assembly pathway of A β *in vitro* and biochemical characterization of A β deposits isolated from AD brains indicate that A β oligomerization occurs *via* distinct intermediates. Recent studies suggest the existence of different types of A β_{42} strains, some causing toxic effects and others aggregation into oligomers without adapting toxic conformations [23]. A β_{40} inhibits amyloid deposition *in vivo* [24], but 3D reconstruction of A β_{1-40} and A β_{1-42} amyloid fibrils revealed similar protofibril structures [25]. The cellular prion protein (PrPC) and amyloid precursor protein (APP)-like protein 1 (APLP1) were suggested as possible mediators of A β -induced synaptic dysfunction [26]. A β oligomers isolated from the brains of AD patients and injected into rodents are capable to disrupt N-methyl D-aspartate acid receptors and impairing memory [27]. A β peptides have a crucial role in regulation of synapse vesicle release and might point to the primary pathological events that lead to compensatory synaptic loss in AD [28]. APLP1 forming heterodimers with APP

and being mainly present on the cell surface, is a strong candidate receptor for (toxic) A β oligomers [29]. They affect the presynaptic and terminal post-synaptic region [30, 31, 424–426], synaptic plasticity and transmission [32] correlating with synaptic loss [33], and perturbed APP synaptic adhesion activity may contribute to synaptic dysfunction and AD pathogenesis [34, 35]. Native amylopherooids isolated from AD brains with a distinct toxic surface induce neuronal loss through a mechanism different from other A β assemblies, which have been reported to perturb glutamatergic synapse transmission [36]. The amount of A β is determined by the balance between its production by proteolytic processing of APP *via* β - and γ -secretases and its clearance. Apolipoprotein E ϵ 4 has been identified as an AD risk factor, partly explained by its reduced ability to crosslink A β [37]. Increased A β production and/or aggregation likely contribute to progression of AD [38], while suppression of A β deposition leads to long-term reduction of AD pathology [39, 40]. Recent results provide a unifying mechanism in which A β oligomers induce τ hyperphosphorylation in AD, while an antibody that targets soluble A β oligomers blocks their attachment to synaptic binding sites and prevents τ hyperphosphorylation [41]. Autoantibodies against A β are common in AD brain and help control the plaque burden [42]. The fraction of the soluble, mainly toxic A β pool is intracellular and is recognized and targeted by conformation-sensitive antibodies [43]. Single-domain antibodies recognize selectively small oligomeric forms of A β , prevent A β -induced neurotoxicity, and inhibit fibril formation [18]. Lipid surfaces promote aggregation of A β proteins and subsequent permeability changes on lipid membranes [44], but there is a dynamic relationship between intra and extracellular pools of A β [45], intraneuronal A β accumulation particularly contributing to AD progression [46], to which changes at neuronal networks may strongly contribute [47].

A prion-like spread has been shown for A β aggregates in a tg mouse model [427], and extrusion of A β aggregates may seed extracellular amyloid plaque formation during AD pathogenesis [428].

Oligomeric and pre-aggregated forms of τ protein have been shown to be toxic *in vitro*, but the mechanisms underlying its structural changes leading to human tauopathies still remain elusive [48, 49]. The natively unfolded character of τ and its aggregation to Alzheimer-like paired helical filaments and the link between A β and τ in this relationship in AD and other NDDs have been discussed conversely (coexistence of both, axonal connection; 'dual pathway' model – [40, 50]. Granular τ oligomers slowly evolve to larger structures and eventually to filaments having a size smaller than those for PHFs purified from AD [51]. Recent studies with τ that has been believed to reside within the cytoplasm, suggested τ aggregates spreading through cell-to-cell transmission of misfolded protein [52–54], and aggregation intermediates are linked to ND [48, 55].

α Syn assembling into highly soluble special oligomers may proceed to insoluble aggregates and plays a central role in ND in Parkinson disease (PD) [56]; it is potentially prone to misfold [57] and may lead to neuronal death, but other modes of toxicity have been proposed [58], suggesting interaction of α Syn and A β resulting in ND [59]. The lysosomal protease cathepsin D influences α Syn processing, aggregation and toxicity *in vivo* [60], and α Syn contributes to glycogen synthase kinase 3 β catalysed τ phosphorylation in PD models [61]. Interaction with synphilin-1 promotes inclusion formation of α Syn providing new insights in to the inclusion body formation in Lewy body disorders [429]. Elevated levels of soluble α Syn oligomers have been detected in post-mortem brains of DLB patients [62]. Seeding induced by α Syn oligomers may lead to spreading of α Syn pathology [63] and to the formation of Lewy body (LB)-like intracellular inclusions [64], with cell-to-cell transmission of α Syn aggregates *via* endocytosis, leading to nuclear fragmentation and caspase-3 activation [65]. NMR spectroscopy provided information about structure and aggregation of α Syn [66]. Methods to detect morphologically distinct oligomeric forms of α Syn have been described [67].

In polyQ diseases, the protein context of expanded polyQ and its soluble mutant conformers are critical for the disease specificity [20]. Structural and dynamic aspects related to oligomerization of superoxide dismutase 1 (SOD1) and its mutants have provided better insight into SOD1 pathway in relation to familial amyotrophic lateral sclerosis (fALS) [68], which is linked to the two genes TARDBP (TDP-43, which encodes TAR-DNA binding protein) and FUS (RNA binding protein fusion) [69, 70], whereas in sporadic amyotrophic lateral sclerosis (sALS) there is lack of evidence of monomer/misfolded SOD1 [71]. As most NDDs, ALS features deposits of SOD1, TARDBP and FUS aggregates.

The discovery of new prions expands the spectrum of their biological functioning [72]. It further promotes the assembly of these pathological conformers into filaments that progressively accumulate in a disease- and protein-specific manner in the cytosol or nuclei of affected brain cells (neurons and/or glia) or in the extracellular space [16, 73]. The relationship between A β and PrPC and

the role of PrPC in the pathogenesis of AD are under discussion [74]. In spinocerebellar ataxia (SCA), protein aggregation, alteration of the CO₂ homeostasis and others are important pathogenic factors [75].

Protein (mis)folding

Proteins are a heterogeneous population of different conformers which, due to their flexibility, are in a dynamic state between various conformational substrates maintained by synthesis and degradation [76]. Folding, part of the normal process that converts newly synthesized proteins to physiologically functional molecules, is controlled by molecular chaperones that prevent inappropriate interaction between non-native polypeptides, and promote the refolding of proteins that have become misfolded as a result of cellular stress [77]. Protein aggregation occurs *in vivo* as a result of improper folding or misfolding leading to a structural change of a normal, functional protein, inducing the formation of protein aggregates with various supramolecular organizations (Fig. 3). Aberrant proteins, the result of production errors, inherited or acquired amino acid substitutions or damage, often cannot fold correctly and will be trapped in misfolded conformations. The pathogenic pathways involve membrane permeabilization through a channel mechanism or hydrophobic interaction of prefibrillary oligomers with various cellular targets [78]. To get rid of misfolded proteins, the living cell contains a large number of intracellular proteases, which, together with the chaperones, comprise the cellular protein quality-control systems in the endoplasmic reticulum (ER). Quality control against misfolded proteins is the cytosole in a network for cell survival [79], and ER protein quality control in NDD is disordered [80].

Many proteins associated with NDDs are intrinsically disordered under physiological conditions [4, 81]. Progressive intracellular protein accumulation can result from various pathological processes: (i) abnormal synthesis and folding, (ii) abnormal interaction with other proteins, (iii) overproduction of protein constituents, (iv) impaired degradation and turnover, (v) altered post-translational modifications of newly synthesized proteins, (vi) protein oxidation, (vii) nucleic acid-induced structural conversions, (viii) abnormal proteolytic cleavage, (ix) improper expression or altered gene splicing, (x) insufficient molecular chaperone activity and (xi) impaired intracellular transport of proteins. Recent studies with mutant huntingtin (mhtt), τ protein and α Syn demonstrated propagation of misfolded protein aggregates through cell-to-cell transmission in cultured cells and tg mouse models [430–432]. Due to the central role of these phenomena in cell biology, protein misfolding and aberrant disorder-to-order conformational transitions in protein structure are associated with a large number of NDDs [82]. Causes are genetic deficits producing a single amino acid substitution or expansion of a repeating amino acid tract, as occurs in familial diseases. However, for most NDDs that occur sporadically or in non-Mendelian familial fashion, other factors may induce the pathogenic cascade.

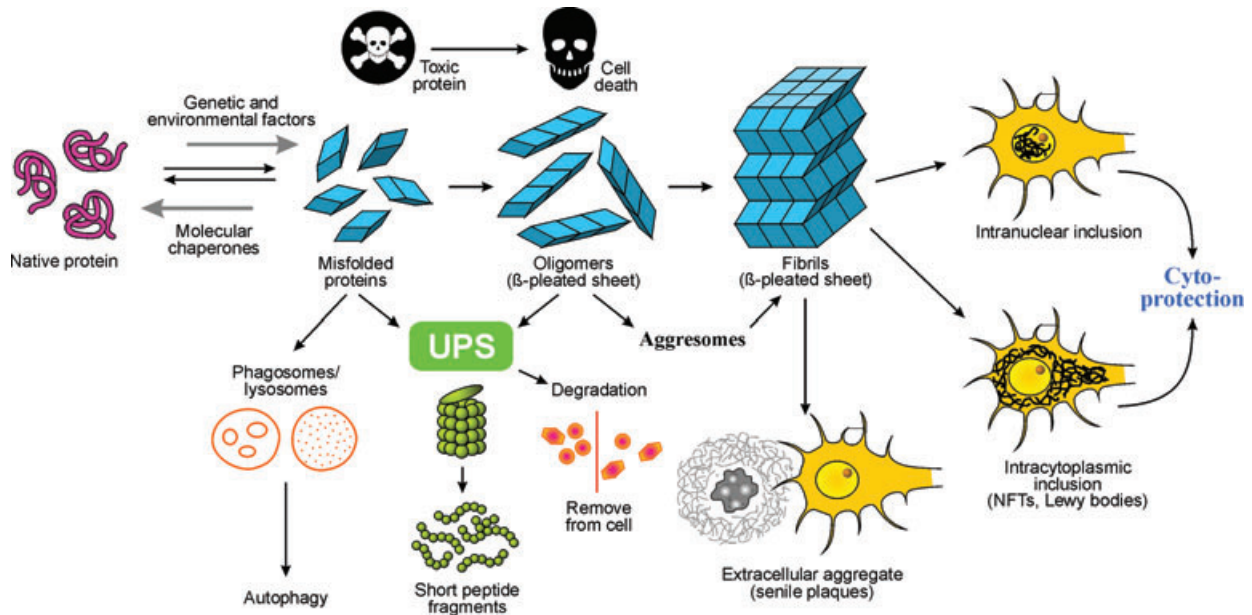


Fig. 3 Model of protein misfolding and fibrillation leading to deposition of aggregated proteins in cells and extracellular spaces *via* actions of the UPS, phagosomes and aggresomes, either causing cell death or cytoprotection.

Proteostasis and molecular chaperones

Protein formation is regulated by the proteostasis network, an integrated biological system that generates and protects the protein fold [83]. Many inherited disorders due to amino acid substitutions exhibit loss-of-function (LOF) pathogenesis because the aberrant protein is eliminated by one of the control systems. However, not all aberrant proteins can be eliminated and the misfolded protein may accumulate and form toxic oligomeric and/or aggregates. In this case, the loss of function may be accompanied by a gain-of-function (GOF) pathogenesis, which often determines the pathological and clinical features [84]. Many diseases of protein homeostasis, or 'proteostasis', due to misregulation of protein maintenance, include LOF and gain-of-toxic-function diseases (AD, PD, Huntington disease/HD). The conformational change may promote diseases either by gain of toxic activity or by the lack of biological function of the natively folded protein under adverse conditions, including OS, ER stress and aging by accumulation of damaged proteins in the cell [85]. In AD, there is no consensus as yet whether the disease acts through a LOF or GOF mechanism. On the other hand, larger protein aggregates may represent an inherent protective or defensive mechanism by sequestering or inactivating toxic oligomers and protofibrils [see 1, 6] and A β monomers have been shown to be neuroprotective. This 'abnormal protein-protein interaction' or 'fatal attractions' hypothesis describes plausible unifying mechanisms to account for the onset and progression of neurodegenerative proteinopathies.

Proteostasis is maintained by a network, which comprises pathways that control protein synthesis, folding, trafficking,

aggregation, disaggregation and degradation, including the unfolded protein response (UPR), the heat-shock response, the ubiquitin proteasome system (UPS) and epigenetic programs [86]. Decreased ability of this network to cope with inherited misfolding-prone proteins, aging, and/or metabolic/environmental stress appears to trigger or exacerbate proteostasis diseases [86]. This is influenced by genes that control aging, thus linking stress and protein homeostasis with the health and life span of the organism. Small molecules can enhance proteostasis by binding to and stabilizing specific proteins (chaperones) or by increasing the proteostasis network capacity (proteostasis regulators) [87]. Adaptation and survival requires the ability to coordinate the activities of protective stress response pathways and chaperone networks.

Molecular chaperones have essential roles in many cellular processes at the folding/degradation interface in mammalian cells [88]. Cellular molecular chaperones, which are ubiquitous, stress-induced proteins, have been found to be effective in preventing misfolding of different disease-causing proteins, essentially reducing the severity of several NDDs and other proteinopathies. Chaperones are engaged in suppressing the effect of protein misfolding-induced consequences [89, 90] inhibiting amyloid formation in the extracellular space [433] and to protect against OS [91]. They play an important role in the deterrence of protein damage during aging and in ND [92]. Conditions of stress are characterized by a robust increase in the synthesis of heat shock proteins (HSPs) that are crucial for recovery from stress-induced protein damage [93]. Almost all HSPs function as molecular chaperones, and the number of diseases that are known to be caused

by their mutations is increasing. Accumulation of aggregation-prone proteins activates signal transduction pathways that control cell viability in various models of PD, HD and ALS [57, 77, 94] and there is an emerging role of chaperones in the pathogenesis of PD [434]. Several chaperone actions might be required to impede tissue pathogenesis *in vivo*, and molecular chaperones may increasingly become new targets for the therapy of NDDs [77].

Protein misfolding and endoplasmic reticulum stress

In neurons, the ER is important for the synthesis, folding and post-translational modification of transmembrane and secreted proteins. The ER response is characterized by changes in specific proteins, causing translational attenuation, induction of ER chaperones and degradation of misfolded proteins, while in prolonged or aggravated ER stress, cellular signals leading to cell death are activated. ER stress may be involved in some human neuronal diseases, such as AD, PD, prion diseases, etc. [95]. The exact mechanisms and causal effects of ER stress and the proteins involved, however, are poorly understood [96].

The mechanism by which α Syn, τ and A β protein make fibrils is an example of conformational plasticity, because these polypeptides can visit a coil or helical structure, but otherwise they convert into a pathogenic β -sheet structure highly suitable for polymerization and fibre formation [57]. Misfolding of α Syn, which is involved in neuronal functions, and can act as molecular chaperone, is a critical factor of synucleinopathies [97]. It can affect the function of several key PD-linked genes such as DJ-1, PINK-1, and perhaps also LRRK2, and parkin, which like α Syn, is also prone to misfolding, especially in the presence of age-related stress [98]. Both conformational folding of previously unfolded τ protein and cleavage causing aggregation lead to neuronal dysfunction by interference with axonal transport, neurotoxicity of early aggregated state, contributing to disruption of neuronal circuits due to synapse loss and cell death [99–101]. Extracellular τ , α Syn and prion aggregates can transmit a misfolded state from the outside to the inside of a cell, indicating propagation of protein misfolding [52, 64, 65].

The role that polyQ-induced aggregates, *e.g.* in HD, plays in disease is not yet fully determined. N-terminal mutant huntingtin (mhtt) proteins activate cellular pathways linked to ER stress and cause protein misfolding inside the cells and form toxic amyloid-like aggregates, preceded by a series of protein misfolding steps termed poly-Q-fibrillation as a prerequisite for the underlying mechanisms of ND [102]. They could be part of a compensatory detoxification process by the cell in which pathogenic oligomers are sequestered [103], suggesting that compounds targeting ER stress may be considered in designing novel approaches for treatment of HD and possibly other polyQ diseases [104].

In vivo, these changes develop insidiously over the lifetime of an individual, even though they usually do not manifest clinically until middle or late life. The causes of this prolonged process due

to progressive damage of specific vulnerable brain regions or neuronal networks before clinical manifestation are poorly understood. A crucial unanswered question is whether these aggregates contribute to the onset and progression of ND are mere bystanders resulting from an alternative pathway, or even may be a neuroprotective response [1, 105]. Although mutations in the genes encoding the fibrillizing proteins segregate familial forms of the corresponding diseases, the same brain lesions also can be formed by the corresponding wild-type protein in a sporadic form of the disease. Since protein misfolding may also result in altering their normal function, *e.g.* physiological proteins, fibrils may be inactive endproducts of a common pathogenic cascade of an otherwise deleterious process, but, in general, detection of fibrillar assemblies indicates that neurons have been exposed to a wide array of noxious agents. It becomes apparent that the pathology of AD and other proteinopathies represents effect rather than cause, or a host response to injury equaling neuroprotection [106].

Unfolded protein response

Proteins are synthesized and folded in the mitochondria as well as in cytosol and in the ER. Alterations in cellular homeostasis that affect protein folding in the ER trigger a signalling pathway known as the UPR [107]. There are three pathways to relieve ER stress and to thus promote survival of the neuron: (i) activation of PRK-like endoplasmic reticulum kinase (PERK) inhibitory cellular protein translation, preventing further protein synthesis; (ii) increased capacity of the ER to handle unfolded proteins, mediated by the activating transcription factor 6, and inositol-requiring kinase-1 and (iii) removal of misfolded proteins from ER by enhancing proteolytic degradation [108]. The molecular mechanisms underlying these and related processes are unclear, but recent studies suggested that the pathway starts with stress detection in the mitochondrial matrix followed by activation of UPR mitochondrial targets in the nucleus. ER stress is caused by disturbances in its structure and function with accumulation of misfolded proteins and alterations in calcium homeostasis [109]. During aging and in NDDs, cellular Ca^{2+} -regulating systems are compromised resulting in synaptic dysfunction, impaired plasticity and ND. OS, perturbed energy metabolism and aggregation of disease-related proteins adversely affect Ca^{2+} homeostasis by mechanisms that have been elucidated [109, 110]. The UPR is activated in pretangle neurons in AD hippocampus [111] and increased levels of molecular chaperones in cytologically normal appearing neurons suggest its early role. Although its initial participation in AD pathogenesis could be neuroprotective, its sustained activation might initiate or mediate ND [112].

Interaction of proteins

Despite differences in the molecular composition of these filamentous lesions, the brain regions and cell types they affect, growing

evidence supports the notion that they engage common downstream pathogenic targets. Although the different localizations of hallmark protein aggregations (extracellular A β deposits in AD, cytoplasmic LBs in PD, TDP-43 intracytoplasmic and intranuclear inclusions in AD, frontotemporal lobar degeneration, ALS, intranuclear inclusions in HD) may suggest that each protein strikes a single cellular domain, recent studies indicate the possibility of common pathogenesis. In addition to showing common morphological and chemical features, the inclusion bodies co-localize with several other proteins that are not structural elements of abnormal fibres, but are binding to them, including various chaperones, proteins implicated in cellular responses, signal transduction, cytoskeletal, cell cycle and others [105, 113]. Proteomic analysis of cortical LBs revealed 296 proteins [114], while in brainstem LBs 90 proteins were identified, differing from Pick bodies and suggesting a complex formation process [115]. *In vivo* protein aggregation exhibits a remarkable specificity, suggesting that conserved mechanisms underlie it depending on selective interactions and result in the formation of fibrillary structures. This might reflect an irreversible sequestration and subsequent loss of functions and/or a failed attempt to refold and degrade aggregated proteins.

The cellular response to these aggregates includes (1) the recruitment of chaperones or proteins involved in the folding of nascent translational products and in the resolubilization of aggregated polypeptides, and (2) the ubiquitination of aggregates, suggesting cellular attempts to degrade deposits of these mutant proteins *via* the UPS [116].

The frequent co-occurrence of AD and PD and of inclusions characteristic of both disorders in several other NDDs suggests the involvement of a common underlying process [117–119], which may be caused by hybrid oligomer interactions [120]. A collision of two or more processes may occur in the same brain region or even within single cells, *e.g.* in rare familial forms of DLB [121]. A direct link between τ and synaptic pathology is supported by accumulation of abnormally phosphorylated τ and α Syn within synaptic terminals in AD brains and APP Swedish mutant tg mice [122, 123]. Induction of hyperphosphorylation of τ by α Syn in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of parkinsonism [124], co-location of phospho- τ and α Syn in both neurofibrillary tangles (NFTs) and LBs [125], and co-occurrence of abnormal deposition of τ , α Syn and TDP-43 in AD, DLB and other NDDs, probably related to genetic factors [118, 126], highlight the interface between these two and other misfolded proteins. Oxidatively modified α Syn degraded by the proteasome promotes the recruitment of τ to protein inclusions in oligodendroglia cells in synucleinopathies [127]. Accumulation of A β and phospho- τ are thought to be coexistent, A β initiating hyperphosphorylation of τ [40]. Both can be linked by separate mechanisms driven by a common upstream driver [50]. Interactions between A β , α Syn and τ may be a molecular mechanism in the overlapping pathology of AD and PD/DLB [128, 129], probably generated by the same stimulus with the outcome possibly having an inverse relationship depending on genetic background or environmental factors. Although recent data documented co-localization of A β

and phospho- τ in synaptosomes [130], and A β and τ protein show synergistic, age-associated effects in triple tg AD mice [131]. Why τ and A β pathologies are so intimately associated, remains one of the major unresolved questions of AD pathophysiology. TDP-43 proteinopathies are distinct from most other NDDs because they are due to protein misfolding without amyloidosis, while TDP-43⁺ inclusions show abnormal hyperphosphorylation, ubiquitination and C-terminal fragments [132]. It is unclear, whether there is a common underlying pathogenic mechanism inducing both ND and fibrillary protein aggregates that are typical for different disease processes (double or triple amyloidosis) or if they represent a common final pathology leading to ND.

The ubiquitin proteasome system

All cellular components are subjected to continuous surveillance by intracellular control systems. The UPS, the major non-lysosomal system for regulating protein turnover, and the autophagy-lysosome pathway (ALP) are the two most important mechanisms for regulating protein handling [133]. These cellular protein quality control systems in the ER are important in the pathogenesis of NDDs, but also in neuroprotection [80, 134]. The presence of ubiquitinated proteins within neuronal inclusions is one of the hallmarks of ND. The inclusions contain various components of the UPS which operates as an intracellular protein-clearing system.

The UPS is a substrate-specific non-lysosomal, ATP-dependent proteolytic system that plays a major role controlling the initial steps of gene expression, DNA repair, nuclear quality-control, cell cycle and signalling control [133, 135]. It appears to be at the intersection of whether a toxic protein is degraded or whether it is packed into an inclusion which may be one of the strategies of the cell to process damaged and/or mutated potentially toxic proteins and that, given a chance, the cell will recover from such stress. Proteasome regulators (activators and inhibitors) have been reviewed recently [136]. Proteasomal dysfunction may be caused by misexpression of one or more of its subunits. The UPS becomes activated during OS and works to process misfolded protein-mediating reactions that link abnormal proteins with multiple ubiquitin (Ub) molecules as a signal for degradation domains and may promote their degradation by Ub ligases [137, 138]. Aggregated proteins are transported to perinuclear microtubule-organizing centres (centrosomes), where they are encapsulated by intermediary filaments to form aggresomes, subsequently subjected to proteolysis and removed by autophagy [139]. Ubiquitylation and endocytosis of plasma membrane proteins are regulated by Ub ligase adaptors [140] mediated by Ub ligase Ubr1 [141]. The proteasome also contains deubiquitinating enzymes that can remove Ub before substrate degradation initiates, thus allowing some substrates to escape degradation [142]. The UPS becomes abnormally activated also during abnormal protein cleavage, and altered or inappropriate gene splicing. In these conditions, it may not be able to degrade damaged proteins producing their aggregation in the cell and ultimately causing neuronal

dysfunction (Fig. 3). A reduction in its efficacy increases the storage of aggregation-prone proteins and could explain the accumulation of Ub and substrates in diseased neurons, which disrupt normal cell activity [116]. However, ubiquitination of protein substrates without proteolysis and proteasome-independent function of Ub in endocytosis and signalling, and Ub-independent proteolytic degradation of proteins have been described [133]. Thus, derangements in the Ub could potentially lead to alterations in processes that are unrelated to protein degradation.

Ubiquitination, the hallmark of protein degradation by the 26S proteasome, is a multistep process, in which Ub-activating enzymes (E1s, E2s and E3s) are key mediators and are able to regulate the chain formation as downstream signalling pathways [137, 143]. Mono-Ub and Ub dimers may regulate the enzymatic functions of Ub carboxy-terminal hydrolase L1 (UCH-L1) and L3, two of the deubiquitinating enzymes expressed in the brain, *in vivo* [144]. The family of proteins containing Ub-like and Ub-associated domains has been implicated in proteasomal degradation, thus regulating the proper turnover of proteins [133] [145]. Control of iron homeostasis is performed by Fe-regulated ubiquitin ligase [146]. Through a process termed sumoylation, SUMO (small Ub-like modifier) monomers are conjugated to target proteins. In some cases they may act to protect proteins from Ub-dependent degradation or appear to trigger polyubiquitination, and there are relationships between Ub, SUMO and DNA repair pathways. Monoubiquitination of the p53 tumour suppressor protein causes it to be transported from the nucleus to the cytoplasm by multifaceted effects of SUMO [133, 147, 148]. p53 protein requires multiple layers of regulatory control to ensure correct functions [435], and p53 proteasomal degradation may be Ub-independent [436]. The complexity of the Ub system in protein regulation and its role in the regulation of cell death are still not fully elucidated [149, 437], but quantitative proteomics gave insight into the function of unconventional Ub chains in proteasomal degradation [150].

Inhibition of lysosomal functions by higher levels of chaperones reduces proteasomal activity [151]. Under conditions of proteolytic stress, the cell may switch to a non-proteolytic form of ubiquitination to help divert misfolded proteins away from an overloaded proteasome, and thus can preserve its proteasomal functions over prolonged periods of stress and recover thereafter [152].

Many expanded proteins are resistant to proteolysis by the UPS, and the lack of its efficacy may be responsible for accumulating expanded proteins within affected cells, leading to *neuronal inclusions*. Ubiquitinated protein aggregates provide a nuclear centre for the formation of inclusion bodies, but there are several differences that distinguish these inclusions, some being aggregated in the cytoplasm, others are prevalent in the nucleus [105]. Differential activities of the UPS in neurons *versus* glia may account for the preferential accumulation of misfolded proteins [153].

Misregulation of degradation of misfolded proteins leads to their accumulation with inhibition of axonal transport, thus facili-

tating the accumulation of ubiquitinated proteins in the cell body and cell dysfunction. This interaction may involve (1) a loss of function, (2) a gain of function or (3) an inflammatory stimulus.

Autophagy and neurodegeneration

Another pathway for cytosolic protein clearance and organelle degradation through lysosomes is autophagy [154–156], a cytosolic, non-specific bulk degradation system, important as a clearance route for many cytosolic, aggregate-prone proteins. Model systems in increasing numbers are available to study the role of autophagy in the central nervous system (CNS) [154, 157]. Proteins are transferred to the lysosomal membrane and, through binding to a receptor lysosome-associated membrane protein (autophagosome), they are translocated into the lysosomal lumen and degraded [158]. Ub has a role in selective autophagy [139]. The molecular mechanism involved in the three autophagic pathways: chaperone-mediated autophagy (CMA), microautophagy (without vesicles) and macroautophagy, the most common type associated with mitochondria and cell death [159, 160]. Macroautophagy is responsible for clearing of aggregated or aggregate-prone proteins, microautophagy for degradation of organelles, and CMA uses the lysosomal protein LAMP2a as a receptor that recognizes proteins with a specific pentapeptide for lysosomal degradation. Their relevance in ND has been reviewed recently [159, 161]. The autophagy machinery is regulated by different types of stress at various levels, from transcriptional activation to post-translation of protein modification [162]. Dysregulation of macroautophagy has been implicated in synaptic dysfunction, cellular stress and neuronal cell death [163] with superoxide being the major ROS regulator [164], and contributes to the pathogenesis of several human diseases, including NDDs [158], while its activation seems to be protective in certain NDDs [165]. The process, known as microautophagy, is poorly understood [166, 167]. Degradation of mutated α Syn by the CMA is impaired, which could explain the selective degeneration of PD dopaminergic neurons [168, 169]. The autophagy-related protein beclin-1 does not only play an important role in the intracellular degradation of α Syn either directly or indirectly through the autophagy pathway [170], thus ameliorating the ND in α Syn models of PD, but also shows reduced expression in early AD [171], while x-box-binding protein, a key UPR transcription factor that regulates genes involved in protein folding and quality control, protects against ALS by increasing autophagy [172]. Tissue-specific impairment of autophagy in the CNS tissue causes massive loss of neurons resulting in ND [173]. Emerging evidence supports the view that induction of autophagy is a neuroprotective process and that inadequate or defective autophagy, rather than excessive autophagy, compromises degradation of UPS substrates and, thus, promotes cell death [174, 175]. The UPS and autophagy are two signalling pathways that can provide protection against ND [138]. However, how autophagy protects cells from damage leading to ND is not yet clear [176, 177].

UPS in neurodegenerative disorders

Dysregulation in the UPS appears to be both a cause and a result of ND processes. Its dysfunction has already been implicated in the pathogenesis of PD [178, 179], and the demonstration that α Syn is degraded by both proteasome and autophagy indicates a possible linkage between the UPS and ALP [168]. Mutated α Syn inhibits ALP by binding to the receptor on the lysosomal membrane for autophagy (Greek: self-digestion) pathway supporting the assumption that the ALP may be related to the development of PD [180]. LBs, the morphological hallmark of PD and DLB, have a distinct central parkin and Ub⁺ domain, with α Syn in the periphery, but it is incorporated into LBs and dystrophic neurites before ubiquitination [181]. Co-localization of α Syn and parkin within LBs suggests that parkin plays a role in ubiquitination and post-translational modification of α Syn [182]. The Parkinson-associated protein PINK1 interacts with Beclin1 and promotes autophagy [438]; on the other hand, PARKIN is cytoprotective, partially by increasing the removal of cellular A β through a proteasome-dependent pathway [439]. There is conflicting evidence concerning the pathogenesis of α Syn aggregation [66]. A functional Ub-3-ligase complex consisting of early-onset familial PD associated Parkin, PINK-1 (PARK-6) and DJ-1 (PARK-7) mutations promotes degradation of un- or misfolded proteins and may constitute a pathogenic mechanism for recessive forms of inherited PD [81, 183]. LRRK2 mutations (PARK8), a major cause of late onset parkinsonism, have clinical features comparable to sporadic PD [184, 185], display variable neuropathology, including α Syn and τ inclusions [186, 187], thus suggesting an upstream role of LRRK2 in protein aggregation [188].

The role of UPS pathology in AD has been reviewed [133, 189]. A β inhibits the proteasome and enhances amyloid and τ accumulation [190], but proteasome inhibition increases accumulation and insolubility of τ protein independent of τ phosphorylation, and JNK inhibition may be partially responsible for the relatively decreased phosphorylation of τ in tg models [191]. ATPase subunit 6b (S6b) transcript up-regulation may be related to tauopathies, while in synucleinopathies it appears not to be involved [192]. The importance of decreased UPS function has been observed also in other NDDs, *e.g.* in HD, where protein quality control regulates polyQ-induced toxicity [20], but its global status in HD brain is not yet fully elucidated [193]. Neuronal polyQ protein inclusions are present predominantly in the nucleus, which is not accessible to autophagy. Intracellular degradation of polyQ aggregates by the UPS is triggered by some nuclear Ub ligases [194], and inclusion bodies are suggested to have a protective cellular response to mhtt mediated by improving intracellular protein degradation [195], while UPS activity in synapses of HD is impaired [196].

Dysfunction of the UPS is also important in ALS showing skein-like inclusions in motor neurons rich in Ub proteasome and some chaperone proteins, in SCAs, with neuronal intranuclear inclusions containing ataxin-1 and several chaperones [197], in ALS-parkinsonism-dementia complex of Guam (ALS/PDS),

neuronal intranuclear inclusion disease, and other NDDs (for review see [133]). However, despite the notion that inclusions might be protective, involved neurons ultimately fail to compensate for the abnormal and/or toxic protein accumulation and, finally, die. While inhibition of the UPS might be expected to worsen most NDDs, its augmentation possesses unique challenges, such as delivery of its components to the nervous system or identification of drugs that enhance the degradation of toxic proteins without compromising normal UPS function [116].

Aggresomes

When the capacity of the proteasome system to degrade misfolded proteins is overwhelmed, aggregation occurs and proteins are moved to a Ub-rich structure termed the 'aggresome' [198]. It forms part of the cellular response to aggregated proteins and appears as inclusions in a number of proteinopathies. Aggresomes have been reported for SOD, parkin, α Syn [181] and prion proteins, the formation of which has been associated with activation of caspases and apoptosis. Ubiquitination and sequestration of protein (*e.g.* α Syn, synphilin-1) in aggresomes and cytoplasmic inclusions may represent a mechanism of cell protection. On the other hand, α Syn aggregation is associated with decline in proteasome and lysosome, which may be involved in the pathogenesis of cell degeneration in PD [199]. However, it is not clear whether aggresome formation is causative or protective [200], although data suggested that they serve a cytoprotective function, facilitating the degradation of toxic proteins.

Oxidative injury

OS occurs when the production of free radicals or their products are in excess of antioxidant defence mechanisms. It can damage biological molecules and initiate a cascade of events, including dysfunction of mitochondrial respiration, excitotoxicity, and a fatal rise in cytosolic calcium leading to cellular dysfunction together with nitric oxide and reactive nitrogen species. Thus, it is a major factor of the cytopathology of many diseases including NDDs and their models [see 201–204]. The generation of ROS during early-stage protein aggregation is a common fundamental molecular mechanism underlying their pathogenesis. A major source of ROS in neurons may result from escaping electrons from the respiratory chain reacting with oxygen. Other contributors are metal-iron-associated Fenton reactions, lipid peroxidation and nitric oxide induced protein nitrosylation [203, 205]. Generation of excessive nitric oxide and ROS can mediate protein misfolding in the absence of genetic predisposition [206]. Among the various free radicals generated in the living organism, hydroxyl radical and peroxynitrite are the most potent and can damage cells *via* non-selective oxidation of proteins, lipids, fatty acids and nucleic acid [204]. They are formed *via* the Haber-Weiss and Fenton reaction

between H_2O_2 and reduced transition metals. Hydrogen peroxide is subsequently converted to hydroxyl radicals by the addition of Fe(II) by Fenton's reaction, one of the fundamental mechanisms underlying neurodegenerative processes. The accumulation and precipitation of proteins may be aggravated by OS, and may, in turn, cause more oxidative damage by interfering with the function of the proteasome, that increases levels of OS not only to proteins but also to other biomolecules [203].

Proteins are initial targets of ROS, and protein radicals generated by ROS can oxidize reduced glutathione, which triggers dysregulation of calcium homeostasis, reactive astrogliosis and other changes observed in ND [207, 208]. Superoxide ($O_2^{\cdot-}$) is suggested to be the major reactive OS regulating autophagy [164]. Cells which fail to compensate for oxidative imbalance (stress) enter apoptosis with rapid cell death, while those with compensatory response to ROS (antioxidant enzymes, low molecular weight reductants, etc.) may show long-term survival. There is no clear and defined mechanism showing how OS plays a key role in the regulation of cell survival and death in NDDs, but sublethal RNA oxidation may be a pathogenic mechanism for NDDs [209].

Increased levels of oxidative damage to DNA, lipids and proteins have been detected in post-mortem tissues from patients with PD, AD, ALS, progressive supranuclear palsy (PSP) and aging, some of which are environment-induced [210]. Oxidative damage to nuclear and mitochondrial DNA (mtDNA) occurs in the earliest detectable phase of AD, PD and HD, but also in normal aging [202, 204, 211–213]. Although the precise sources of increased oxidative damage are not fully clear, increased localization of redox-active transition metals in brain regions most affected by ND is consistent with their contribution to OS. Free radical oxygen chemistry plays an important pathogenic role in all these conditions, though it is as yet undetermined what types of oxidative damage occur early in the pathogenic cascade and which ones are secondary manifestation of dying neurons [214, 215]. HSPs have been shown to protect against OS [91].

Metals and oxidative stress

Alterations in metal homeostasis inducing increased production of free radicals, suggests a direct cause-effect relationship between disruption in metal homeostasis and the increased oxidative damage. In addition to the generation of $O_2^{\cdot-}$ and H_2O_2 , the availability of redox-active Fe is a major determinant of ROS-mediated cellular damage. Elevated levels of redox-active Fe, derived from degenerating mitochondria, accumulate in the normal aging brain and in several NDDs [216].

Iron is a powerful promoter of free radical damage, able to catalyse generation of highly reactive radicals from H_2O_2 and lipid peroxides, generating OS. Although most iron in the brain is stored in ferritin, 'catalytic' iron is readily mobilized from injured brain tissue. In AD, aberrant metal homeostasis may contribute to the formation of ROS and toxic A β oligomers, and increased lipid peroxidation precedes A β plaque formation in animal models of AD. Imbalance in iron homeostasis is a precursor of the ND

process leading to AD [440]. Conditions such as neuroferritinopathy [217] and Friedreich ataxia are associated with mutations in genes that encode proteins involved in iron metabolism [218], inducing OS and cell death [441] the brain ages, iron accumulates in regions that are affected by AD and PD [219], and dopamine (DA) complexes of iron are important in the pathogenesis of PD [220].

Oxidative stress in Alzheimer disease

The role of OS in various NDDs, including AD and PD, has recently been reviewed [see 1, 221]. Here, only some essentials will be summarized.

In both human AD and transgenic (tg) mouse models of AD, oxidative damage occurs preceding A β deposition that further contributes to OS and ND [222]. In the initial stages of AD, A β deposition and phospho- τ may represent compensatory responses to ensure that neurons may not succumb to oxidative damage. OS induces macroautophagy of A β protein and ensuing apoptosis [223]. Mutant APP and its derivatives are involved in the generation of free radicals in mitochondria and cause mitochondrial oxidative damage, linking A β , generation of free radicals and oxidative damage in the pathogenesis of AD [224]. OS or neurotoxic by-products of lipid peroxidation may damage DNA and lead to programmed cell death (PCD) in AD. In AD and other NDDs, the production of advanced glycation end products (AGEs) and their receptors has been observed [225–227]. Being both markers of transitional metal-induced OS and inducers of protein crosslinking and free radical formation, they may reflect early disease-specific changes rather than late epiphenomena. AGEs co-localize with inducible nitric oxide synthase in AD, supporting an AGE-induced OS [227]; and contribution of AGE receptors (RAGE) to A β cytotoxicity [228], while infusion of soluble RAGE in tg animals decreases A β content and amyloid load [225]. Oxidative imbalance is met by a series of complex reactions (mitochondrial dysfunction, impaired synaptic transmission, disruption of membrane integrity, etc.) to establish a disease-related homeostasis balance [204]. Excess A β may induce OS and/or disturb cellular calcium homeostasis through disproportionate PrPC-receptor crosslinking, but the precise mechanism between mitochondrial oxidative damage and the role of oligomeric A β has not yet been explicated [229]. Oxidative damage to DNA and RNA repair is particularly severe in the hippocampus, the earliest and most severely involved brain area, and nitrated brain proteins are seen in both early and late stages of AD [230]. In AD RNA is extensively modified and, while clearly damaged, its rapid turnover may also serve a protective function [204]. Stress-activated protein kinase pathways triggered by OS, are excessively activated in AD, even in early stages, deregulating cyclin-dependent kinase 5, compromising the cellular antioxidant defence system and causing mitochondrial damage [231]. S-nitrosylation of dynamin-related protein 1 (Drp1) that is increased in AD brains, mediates A β -related mitochondrial fission and neuronal injury [232]. Antioxidants may protect neurons in AD and PD, reducing the risk of ND [233].

Oxidative stress in Parkinson disease

In PD, many biochemical changes indicate compromised antioxidant systems suggested to underlie cellular vulnerability to progressive OS which generates excessive ROS or free radicals in substantia nigra (SN) with subsequent cell damage [see 234–237]. Increase of iron in the SNp with a shift of Fe(II):Fe(III) of 2:1 as compared to 1:2 in controls and aggregation of τ , can promote DA synthesis with accompanying increased generation of reactive metabolites, leading to degeneration. Protein misfolding of sporadic PD has been associated with ROS formed as products of O₂ reduction by combination of DA and Fe [220]. In pigmented DAergic neurons of human substantia nigra pars compacta (SNc) recent proteomics have identified L-ferritin in neuromelanin granules, suggesting it as an important player in the complicated network governing Fe homeostasis in human DA neurons [238]. Both reduced glutathione, and glutathione peroxidase activity are decreased in SN of PD and in incidental LB disease (preclinical PD), probably preceding both complex I and DA loss [239]. Peroxynitrite, formed by reduced SOD, induces aggregation of α Syn *in situ*, and nitrated α Syn is found in the core of LBs indicating their in damaging structural proteins [236]. Cross-linking of α Syn by AGEs in PD and in incidental LB disease suggests that AGE-promoted LB formation may reflect early disease-specific changes, accelerating inclusion body formation [240]. Protein misfolding in sPD has been associated with ROS as products of O₂ reduction by combination of DA and Fe [220]. Abnormal α Syn as found in LBs produces hydrogen peroxide and the neurons are capable of dissecting antioxidant enzymes to regions of OS, and that glutathione peroxidase-positive microglia are involved in neuroprotection in PD and DLB [241]. α Syn is up-regulated in a subset of neurons in response to chronic OS and is associated with neuroprotection from relatively low levels of OS. Formation of α Syn protofibrils is stimulated by translational modifications that occur under conditions of OS, while its aggregation is inhibited by antioxidants and various proteins with chaperone activity [242]. Many of the above factors demonstrated in Human PD and animal models indicate a multicomponent process in this NDD [see 243] and cell death pathways in PD are caused by many interacting factors [244, 245].

Oxidative stress in other neurodegenerative disorders

OS is also recognized as a major pathogenic factor in other NDDs [see 1]. In HD, where in both human brain and in tg mouse models, increased indices of OS markers have been reported, the crucial initiation mechanism induced by mhtt is still unclear, but early and critical involvement of defects in mitochondrial function and CNS energy metabolism may trigger the disease. Proteomic and OS analyses in human brain samples of HD indicate that OS and damage to specific macromolecules would participate in disease progression [246].

In PSP, increased lipid peroxidation in cerebral cortex [247] is proportional to the extent of τ pathology, increased activity of antioxidant systems, *e.g.* SOD and glutathione, is seen in multiple brain areas, and oxidative damage affects regions vulnerable to PSP and argyrophilic grain disease [248]. Increased OS is important in both sALS and fALS. The two principal hypotheses on the pathogenesis of ALS are: (i) oxidative damage stemming from aberrant SOD1 redox chemistry, and (ii) misfolding of the mutant protein. Enhanced basal oxidoradical products, lipid peroxide, perturbed calcium homeostasis and increased nitrotyrosine in lower motoneurons of both tg mice and human ALS are present. At terminal stages disruption of glutathione peroxidase PrxII/GPxI-overexpression mechanism was observed, suggesting that the breakdown of this redox system accelerates neuronal degeneration and/or death. Because only a subset of ALS cases can be attributed to one particular deficit, *e.g.* mutation of SOD1, ALS aetiology is likely to be multifactorial [249]. Mutant SOD1 localized in the intermembrane space of mitochondria is sufficient to determine mitochondrial abnormalities and neuronal toxicity, thus contributing to ALS pathogenesis [250, 251]. Extracellular mutant SOD1 induces microglial-mediated motoneuron injury [442]. Two genes have recently be linked to fALS–TARDP (TDP-43) and FUS (RNA binding protein fusion [69, 70], which comprises 3% and 4% of fALS, respectively. sALS has been associated with ECP3 gene, which encodes the catalytic subunit of the histone acetyltransferase complex elongator protein [69]. Identification of mutations in the gene encoding TDP-43, identified in both fALS and sALS stress the importance of TDP-43 in the pathogenesis of both types of ALS [252], but the precise mechanisms by which SOD1 leads to ND have not been defined. OS and cytoskeletal abnormalities causing increased protein glutathionylation leading to abnormalities in neuronal function are essential in Friedreich's ataxia [218].

In summary, free radical-mediated damage to lipids, proteins and nucleic acids is at least a part of the pathogenic events in the majority of NDDs. OS should be considered a window to view both some of the basic pathogenic cascades leading to ND as a means to design strategies to modify fundamental abnormalities, preventing or delaying disease progress. Induction of heat shock proteins has recently been suggested for protection against OS [91].

Impaired bioenergetics and mitochondrial dysfunction

Mitochondria, the 'energy powerhouse of the cell', are key cytoplasmic organelles vital for the function and survival of neurons. They provide energy from aerobic metabolism; oxidative phosphorylation *via* the oxidative phosphorylation system (OXPHOS) is the principal source of high-energy compounds [253]. These proteins link mitochondrial function and dynamics to the regulation of metabolism, cell-cycle control, development and cell death, giving

evidence that provide molecular definition to mitochondria as a central platform in the execution of diverse cellular events, including cell death [254, 255].

Mitochondria are both targets and important sources of ROS. Generation of reactive oxidants, including ROS, is increased in damaged mitochondria and in cells with compromised mitochondrial function. Due to the heterogeneity of NS mitochondria and variations in mitochondrial functioning related to regionally distinct regulatory influences and dependence of their energy production to local demands, they show selective vulnerability to injury [256]. Recent studies have shown that healthy aging is associated with reduced neuronal mitochondrial metabolism and altered glial mitochondrial metabolism, which may be in part responsible for decline in brain function [443]. High levels of oxidants can induce the mitochondrial permeability transition, uncouple oxidative phosphorylation with catastrophic effects on mitochondrial energetics, and contribute to cytotoxicity *via* necrosis and/or apoptosis. Two major mechanisms of mitochondrial damage are the respiratory chain enzyme and mitochondrial DNA. OS and damage to mtDNA during aging impair mitochondrial energy metabolism and ion homeostasis in neurons, thereby rendering them vulnerable to degeneration [253, 257]. Disturbances of the mitochondrial proteolytic system affect neuronal maintenance and axonal function [444]. In NDD, there is a reciprocal interaction between mitochondrial fusion, fission, transport and mitophagy [258]. Impaired bioenergetics and dysfunction of mitochondrial energy metabolism lead to reduced ATP production, impaired calcium buffering and generation of ROS, representing a 'deadly triad in ND' [259]. Mitochondrial dysfunction initiates and propagates neuronal dysfunction in all age-associated NDDs [445].

In a variety of tissues, cumulative OS, disrupted mitochondrial respiration and oxidative mitochondrial damage are associated with, and may promote cell death [203, 253–255, 259]. Dysfunctions of mitochondria disturb cell function, cause mtDNA damage, sensitize cells to neurotoxic insults and may initiate cell death, all significant phenomena in the pathogenesis of NDDs [253, 257, 260]. The mtDNA may play an essential role in the pathogenesis of HD, that shows multiple mtDNA deletions in over 60% of HD patients, probably caused by CAG repeats instability and mhmt [261], that directly and indirectly impairs mitochondrial function [262].

OXPPOS disorders ranging from *Leigh disease* to PD and AD are caused by defects of mitochondrial energy metabolism, related to complex I deficiency [263]. There are several pathways by which both mitochondrial dysfunction and protein aggregation may interact (Fig. 4). Both aggregated SOD and A β in the mitochondrial matrix could contribute to cell death. The mitochondrial permeability transition pore, being crucial in both necrotic and apoptotic cell death, is controlled by anti-apoptotic members of the Bax/Bcl-2 family [264]. Mitochondrial Bax interacts with the voltage-dependent anion channel to accelerate opening of the permeability transition pore which is favoured by Ca²⁺ and oxidizing agents, contributing to cytochrome c release. Calcium regulation controls mitochondria motility and morphology in steady state,

stressed and pathological conditions [265, 266]. A consequence of mitochondrial dysfunction is increased generation of free radicals and oxidative damage [254].

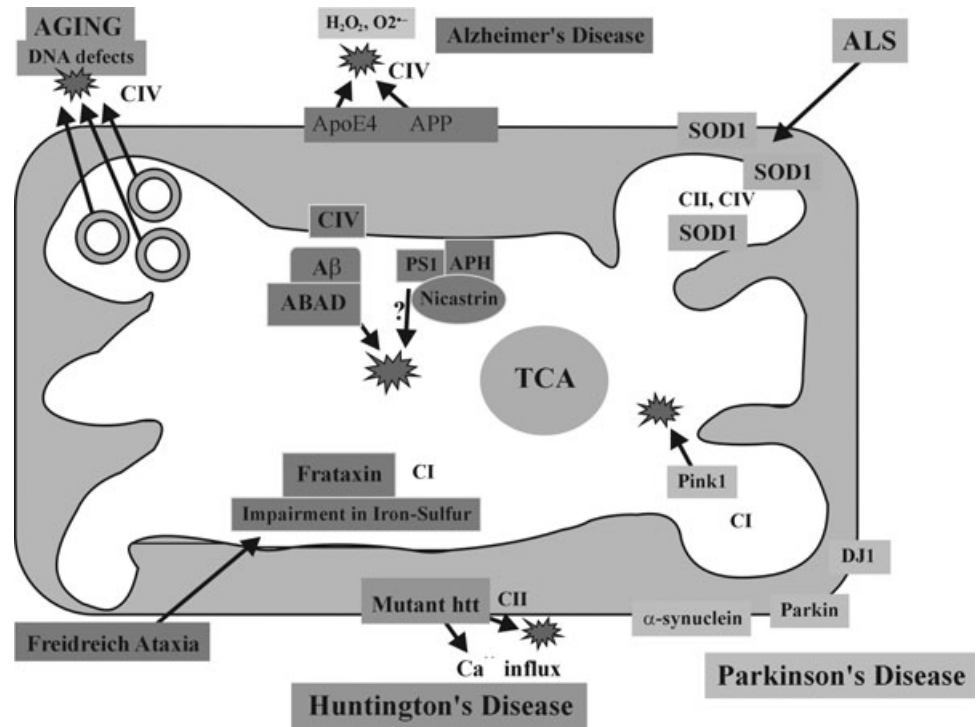
A decrease in the DNA base excision repair activity in NDDs suggests that the brain might be subjected to the double insult of increased DNA damage, as well as deficiencies of DNA repair pathways [267–269]. There is evidence of impaired DNA repair in both the aging brain and AD [270]. Although the molecular basis underlying the decline in mitochondrial function is not really understood, recent experimental evidence has shed some light on the pivotal role of mitochondrial morphology control and dysregulated mitochondrial fusion and fission events in ND [271]. Whether these changes are a secondary consequence of other factors or whether they cause eventual cell death is unknown. However, the identification of mutations in genes that encode proteins functioning in DNA repair and damage establish a mechanistic precedent that clearly links DNA damage and repair anomalies with progressive ND [268].

The importance of microRNAs, brain-enriched, small non-coding RNAs that participate in RNA translational and protein expression regulation, has been emphasized [272], suggesting their involvement in the emergence or progression of NDDs, including AD and prion-induced NDD [273–276].

Mitochondrial dysfunction in Alzheimer and Parkinson disease

In AD, there is a large body of evidence implicating impaired energy metabolism and oxidative damage [see 204, 209]. AD brains show an average 50% reduction in mtRNA content that, together with other changes, is likely to reduce oxidative phosphorylation. The 'mitochondrial cascade hypothesis', that has recently been updated, could explain many of the biochemical, genetic and pathological features of sporadic AD [277, 278]. Significant increase in oxidative damage to mtDNA in AD brain may cause abnormal mitochondrial dynamics and dysfunction that ultimately damage AD neurons [279]. A β plays a role in the formation of mitochondrial permeability transition pore (mPTP) [446]. A β -induced mitochondrial dysfunction is an early event in AD tg models [280] and is a trigger of AD pathophysiology [447]. Patterns in protein changes in early AD suggest activation of mitochondrial pathways that include proteins responsible for transport and utilization of ATP. The most prominent changes may occur in early AD [448]. Despite the evidence of mitochondrial dysfunction in AD, no causative mutations in the mtDNA have been detected so far, and results of studies on the role of mtDNA haplogroups in AD are controversial, although a primary role of the mitochondrial genome is suggested [278]. Both APP and γ -secretase, as well as an isoform of insulin-degrading enzyme, which regulates A β levels, are present in mitochondria [224], and mitochondrial OS causes hyperphosphorylation of τ [281]. Mitochondrial dysfunction in AD is caused by oligomeric A β [449], leading to impairment of ATP production and increase of OS. It may also be

Fig. 4 Schematic interaction of proteins in neurodegenerative diseases and mitochondria. Accumulation of mitochondrial DNA mutations may induce ROS production and cause oxidative damage in aging. In AD, ROS production and decreased ATP may contribute to production of A β peptides that may enter mitochondria, induce free radicals, decrease cytochrome oxidase activity and inhibit ATP generation. APP is transported to outer mitochondrial membranes, blocks import of nuclear cytochrome oxidase proteins to mitochondria, and may decrease cytochrome oxidase activity. In AD and models, A β is found in mitochondrial matrix, produces free radicals and causes mitochondrial dysfunction. N-terminal portion of ApoE4, γ -secretase complex proteins, *e.g.* presenilins and nicastrin, associated with mitochondria, may contribute to A β production and cause oxidative damage. In HD neurons, Htt binds to outer mitochondrial membrane and induces free radical production; H₂O₂ may also interrupt calcium uptake. In PD neurons, mutant proteins of α Syn, Parkin, PINK1 and DJ1 are associated with mitochondria and cause their dysfunction. In ALS, mutant SOD1, localized in inner and outer mitochondrial membranes and matrix, induces oxidative damage; associated with impairment of complexes II and IV. Frataxin, a gene product in FRA, is a mitochondrial protein responsible for heme biosynthesis and formation of iron-sulfur clusters, facilitating the accumulation of iron and inducing free radicals (modified from [257]).



caused by impaired axonal transport with proximal collection of mitochondria which could contribute to loss of distal synapses [282]. Calcium dysregulation occurring early in AD, related to PSEN mutations, A β production and tau phosphorylation [450] leads to synaptic and neuronal dysfunction, underlying dementia associated with the disease [451]. Caspase-cleaved τ expression results in mitochondrial dysfunction in cortical neurons *via* increased calcineurin activity in AD brains [283]. Significant increase in oxidative damage to mtDNA in AD brain may cause abnormal mitochondrial dynamics and dysfunction that ultimately damage AD neurons [279]. Mitochondrial ATP synthase in the entorhinal cortex is a target of OS in the first, clinically silent periods of AD pathology [284].

Mitochondrial alterations and OS are important parts of the multifactorial pathogenic process of PD [267, 285–288, 452]. In both sPD and fPD, abnormal mitochondrial paradigms include impaired function of the electron transport chain, damage to mtDNA, impaired calcium buffering, and anomalies in mitochondrial morphology and dynamics. Mitochondrial dysfunction triggers an increased free turbulin, which destabilizes the microtubule network and promotes α Syn oligomerization [453]. Since the UPS requires ATP at several steps, impaired mitochondrial

function may impair its activity. More importantly, increased production of ROS leads to damaged misfolded proteins requiring degradation by the UPS. Parkin plays a role in maintaining mitochondrial homeostasis [289]. It improves mitochondrial dysfunction, alters the intrinsic threshold for mitochondrial cytochrome c release, regulates their remodelling, promotes their autophagy, promotes DNA repair and protects against genotoxicity, promotes intracellular A β ₄₂ clearance [289–293] and regulates DNA repair [294], while PINK1 (PARK6), a fPD-associated gene, modulates mitochondrial morphogenesis and distribution [295]. Both are causes of autosomal recessive PD and induce the autophagic pathway (mitophagy) or defective oxidative phosphorylation [454, 455].

A specific protein–protein interaction of α Syn and COX, a key enzyme of the mitochondrial respiratory chain, suggests that α Syn aggregation may contribute to enhanced mitochondrial dysfunction [296].

Acute action of rotenone induces mitochondrial ROS production disrupting Ca²⁺ homeostasis in SNc but not in substantia nigra pars reticulata (SNr) neurons [297]. Both rotenone and chronic MPTP result in oxidative damage [298, 299] and α Syn aggregates closely resembling LBs, which were not reproduced by

others [300, 301]. Mitochondrial complex I inhibition is not required in the models for DAergic cell death [302]. Subacute rotenone treatment of SH-SY5Y neuroblastoma cells reproduced Lewy neurites but not LB inclusions, reduces mitochondrial movement and slowly kills neural cells [303]. Mutations in parkin which cause recessive early-onset PD, are associated with marked mitochondrial abnormalities and less resistance to OS induced by paraquat. Reduction of cerebral mitochondrial metabolism is seen in early PD, but whether mitochondrial dysfunction is a primary or secondary event, or part of a multifactorial pathogenic process remains to be elucidated [267]. mtDNA abnormalities and mitochondrial dysfunction are implicated in PD pathogenesis, and a link between mitochondrial dysfunction, OS, protein misfolding and abnormal autophagy is becoming increasingly prominent [304].

For clarification of NDDs with genetic causes of bioenergetic deficits see [1]. Energetic defects in major NDDs only in part have been proven by the identification of genetic defects that are causally linked to mitochondrial dysfunction. If this has a causative role to disease pathogenesis, then a number of therapeutic targets are implicated, including the permeability transition pore, cytochrome c release, free radical scavengers that could result in novel treatments. Mhtt causes calcium homeostasis and mitochondrial dysfunction in striatal neurons and excitotoxic neuronal death [305, 306, 456], and in models of Machado-Joseph disease, decreased synthesis of the protein Hsp27 and increased mitochondrial DNA damage are seen [307, 308]. Mitochondrial dysfunction has been linked to the ALS variants of SOD1 which is preferentially associated with mitochondria and subsequently impairs mitochondrial function [457] *via* the mitochondrial permeability transition pore (mPTP) [458].

Fragmentation of neuronal Golgi apparatus

Fragmentation of the neuronal Golgi apparatus—probably a secondary effect of the above mentioned basic mechanisms – was reported in ALS, corticobasal degeneration, AD, PD, Creutzfeldt-Jakob disease, and in SCA type 2 (SCA2) [309]. Mechanisms involved in Golgi fragmentation include: (i) dysregulation by mutant SOD1 of the microtubule-destabilizing protein Stathmin, (ii) disruption by mutant SOD1 of the neuronal cytoplasmic dynein, (iii) coprecipitation of mutant SOD1 with Hsp25 and Hsp27, (iv) reduction of detyrosinated microtubules by aggregated τ which resulted in non-apoptotic cell death and (v) disruption by mutant growth hormone of the trafficking from the rough ER to the Golgi apparatus [310]. α Syn has been shown to block ER Golgi traffic causing Golgi fragmentation and neuronal Golgi fragmentation is an early and probably irreversible lesion in ND in nigral neurons with α Syn⁺ inclusions in PD [311], caused by a variety of mechanisms including accumulation of misfolded proteins.

Disruption of cellular/axonal transport

There is growing evidence that defective neuronal and axonal transport due to early axonal dysfunction play a mechanistic role in most NDDs [282, 312, 313]. Whether misregulation of axonal transport has a direct role in the pathogenesis of these disorders or is a secondary phenomenon remains to be elucidated. Most of the transport uses the microtubule system that is stabilized by dystrophin [314] and forms a network of trafficking highways. Cargo is linked to the cytoskeleton by unidirectional proteins made of a motor domain that reversibly interacts with the cytoskeleton and converts chemical energy into motion. All axonal components are synthesized in the cell body and transported from there into the axonal processes (anterograde transport). A complementary mechanism transports cargo in the opposite direction, *i.e.* away from the axon into the cell body (retrograde transport). It is powered by members of the kinesin protein transport family, fast retrograde and slow anterograde transport, *e.g.* of neurofilament proteins, by dynein and is regulated by neurofilament subunit head domain phosphorylation [315–317]. Slow transport is a function of neuronal intermediate neurofilaments [318]. For intracellular transport which is fundamental for cellular functions, survival and morphogenesis, the kinesin superfamily transport proteins are important [319]. Neurofilament light chain head domain phosphorylation regulates axonal transport of neurofilaments [315].

Three mechanisms highlight the significance of disrupted cellular/axonal transport in human NDDs: (i) human motor protein mutations in these disorders, (ii) axonal transport defects in animal and *in vitro* cellular models harbouring human mutations and (iii) roles for pathogenic proteins like APP, τ , presenilin and synuclein, in the regulation of axonal transport [320]. The main pathogenic stimuli of these conditions, though often not definitely determined, result in an initial perturbation of the axon and its cytoskeleton, which then results in slow neuronal degeneration and loss of connectivity [312]. Mitochondrial transport in axons uses motors of kinesin families and cytoplasmic dynein, to translocate along microtubules, and bidirectional movement may be coordinated through interaction between dynein and kinesin-1. Protein defects that are directly or indirectly linked to axonal transport could be reversed by specific interventions stabilizing microtubules and repair or protect axons. The axonal transport of τ occurs *via* a mechanism utilizing fast transport motors, including the kinesin family of proteins, and that α Syn transport in neurons may involve both kinesin and dynein proteins [313].

Axonal transport in tauopathies

Axonal transport is impaired in AD and other tauopathies [321, 322], probably early in their pathogenesis. Proteolytic cleavage of APP occurs before its sorting into axonal transport vesicles [323]. It travels *via* fast axonal transport and in vesicular complexes containing presenilin and β -site APP-cleaving enzyme 1 (BACE1) and

acts as a receptor for the anterograde motor kinesin. Decreased retrograde transport of nerve growth factor (NGF) in human brain and mouse models leads to loss of neuronal markers and shrinkage of neurons in the cholinergic basal forebrain, rather than due to decreased synthesis. Misregulation of APP can transduce into misregulation of fast axonal transport, which is a pathogenic mechanism for intraneuronal A β [324]. There are multiple initiating factors converging upon pathways of amyloid induced defects in neuronal transport [325]. τ , is a microtubule-binding protein that, after its hyperphosphorylation and segregation into tangles, is unable to bind microtubuli, causing their destabilization and, thereby, disrupting axonal transport movement. The 3- and 4-repeat τ proteins show differential effects on mitochondrial axonal transport [326]. Interfering with axonal transport may activate stress kinase pathways initiating a biochemical cascade that drives normal τ proteins into a pathogenic state [327]. However, axonal transport rates *in vivo* are unaffected by τ deletion, or hyperexpression, in mice [328].

Axonal transport in synucleinopathies

α Syn is a highly conserved protein, strongly expressed in neurons and enriched in presynaptic terminals. It is mainly transported in the slow, but a part also in fast transport. Significant age-related transport retardation may lead to accumulation of α Syn over time and produces pathology suggesting axonal transport abnormalities in synucleinopathies [329]. Accumulations of small α Syn aggregates in presynaptic terminals in the cortex of DLB and PD associated with loss of dendritic spines suggest a pathological impact on synaptic functions leading to ND, implicating PD as a synaptopathy [330].

Axonal transport in other neurodegenerative diseases

In SOD-1 tg models of ALS show retarded transport of neurofilament proteins and deficits in the delivery of mitochondria to the axon by fast transport, even before symptom onset implicated impaired transport as an early defect in the progress of ND, but, to date, no motor protein gene mutation in human ALS has been reported [331]. Mutant SOD1 interfering with axonal transport and protein turnover may influence the function and viability of motor neurons in ALS [332].

HD shows striatal degeneration with aggregation of huntingtin (htt) within vesicles and moves in the fast axonal transport component. In animal models, this was inhibited by infusion with pathological polyQ repeats and by disruption of the *Drosophila* htt gene. Htt plays a role in protein trafficking, vesicle transport, post-synaptic signalling, transcriptional regulation and apoptosis. A loss of function of the normal protein and a toxic gain of function of mhtt contribute to the disruption of multiple intracellular pathways [193]. An htt-binding protein HAP1 interacts with the

dynactin complex, important for dynein and possibly kinesin fast movements, and accumulated vesicles and organelles in dystrophic axons from human HD patients suggest that aggregates of polyQ repeats disrupt fast axonal transport, and there is enhanced sensibility of striatal neurons to axonal transport defects induced by mhtt [333].

Dysfunction of neurotrophins

There is growing evidence that reduced neurotrophic support is a significant factor in the pathogenesis of NDDs [334]. NTFs affect neuronal survival; influence synaptic function and plasticity. NTFs bind to different receptors, to a common receptor, and each of them also binds to one of the family of Trk receptors. Since NTFs in neurons are subject to retrograde and to anterograde transport from and to targeting neurons, their effects may be related to synthesis in local or remote sites or to changes in axonal transport. In CNS disorders, such as AD, PD and HD, OS appears linked to the loss of neurotrophic support [201]; it can cause down-regulation of NTFs which, in turn, up-regulates antioxidant enzymes and promotes the expression of antioxidant proteins. Brain-derived neurotrophic factor (BDNF) levels in tg mouse models of AD are negatively correlated with A β levels, suggesting that the effect of A β on decreased BDNF expression is specific to the aggregation state of A β and is dependent on large oligomers [335]. AD brain shows increase of the precursor form of NTF and decrease in BDNF in surviving neurons of hippocampus and neocortex, and decrease of TrkA in cortex and nucleus basalis [321]. A β may induce the TrkA pathway activation and promote NGF secretion [336, 337]. A β may act as a neurotrophic factor that mimics the activity of NGF. However, at higher concentrations, the amyloid behaves as an antagonist of NGF, contributing to the advent of AD [338]. A β ₄₂ may induce neuronal death through the p75 NTF receptor, and p75-A β -PrPC complexes could provide reactive OS and elevated intracellular calcium required for p75 signalling [339]. Post-mortem studies point to a lack of NGF action in early AD stages, whereas NGF is found in enhanced concentrations in brains with severe AD partly due to a pathologically altered axonal transport of NGF in the neurons [340]. Advanced glycation and lipoxidation end-products modification of pro-NGF offers a novel pathway in the etiopathogenesis of AD [459]. Inhibition of soluble NTF signalling in a mouse model of AD prevents/slows pre-plaque amyloid-associated neuropathology, and potentially the progressive neuron 'loss' in AD [341, 342].

New steps and targets in the pathogenesis of AD may be: NGF and BDNF signalling through neurotrophic tyrosine kinases prevent the cleavage of APP by BACE1, which, together with γ -secretase, converts APP into toxic forming A β fragments, and a soluble N-terminal fragment (N-APP). In AD, this extracellular fragment of APP, and death receptor G may engage tumour necrosis factor (TNF) receptor family member 21 (TNFRSF21) which activates a widespread caspase-dependent self-destructing process – *via*

activating caspase-6 apoptosis-related cysteine peptidase (casp6, MCH2)-related enzymes—as a major culprit behind AD [343]. This pro-apoptotic pathway proposed by these data may be relevant for other NDDs.

Studies in rodent and primate models of AD showed that BDNF prevents lesion-induced death of entorhinal neurons, reverses neuronal atrophy and ameliorates age-related cognitive impairment. $\text{A}\beta$ -induced NGF dysmetabolism in AD may explain the paradoxical up-regulation of the precursor form of NGF (pro-NGF) in AD accompanied by atrophy of forebrain cholinergic neurons [344]. Protectional effects of BDNF on cortical neuronal circuitry involving AD, acting through amyloid-independent mechanisms [345], indicate a prominent role of NGF in both the aetiology and treatment of AD [346].

In PD, decreased neuronal content and their receptors in SN indicate a reduction of neurotrophic support and alterations in axon guidance in early stages of cellular stress, leading to dopaminergic cell death [334]. In HD, the mhtt induces a down-regulation of BDNF in the basal ganglia, leading to neuronal loss, opening up the possibility of BDNF therapy. Transcription from BDNF promoter II and IV is down-regulated in human HD cortex from an early symptomatic stage. In addition to the reduction in BDNF mRNA, there may be unbalanced neurotrophic receptor signalling in HD [347]. In ALS, NGF concentrations and BDNF are up-regulated in early stages of the disease, whereas the levels of other NGFs gradually increase during the course of the disorder. In ALS spinal cords, TrkA was up-regulated, but the results of trials in both animal models and human patients were controversial. Therefore, comparative *in situ* data for transcription levels and protein contents in NTFs and their receptors in both sites of neuronal origin and termination in human brain are needed to understand their potential role in new treatment strategies [201, 345].

‘Neuroinflammatory’ processes

Chronic inflammatory reactions and signs of immune activation in the CNS, with major histocompatibility complex (MHC) class II expression, glial reaction, T-cell infiltration, and blood-brain barrier dysfunction are prominent pathological features in the pathogenesis and progression of NDDs [348]. Iron has various pro- and anti-inflammatory activities, and inappropriate iron chelation may be a major pathogenic contributor to inflammatory and NDDs [349]. AD ‘inflammation’ has been considered toxic or, on the contrary, useful [350]. However, a better knowledge about the interplay between the nervous system and the local and systemic immune system will be important for the understanding of pathogenic mechanisms of ND [351], the role of innate ‘protective autoimmunity’ and of reparative functions of autoimmunity in NDDs [352]. It has been suggested that immune alterations may occur prior to amyloid deposition and neuronal degeneration. Complement activation exacerbates the pathology of AD, and it

has been discussed whether it could be the outcome of the innate immunity defence in the brain [353]. A central question is whether immune and inflammatory pathways become hyperactivated with age and promote ND or whether insufficient immune responses, which fail to cope with age-related stress, may contribute to NDDs [354]. Age-related neuroinflammatory changes negatively impact neuronal function [460]. Breakdown of the normal blood-brain barrier with influx of blood-born molecules (plasma proteins) have been suggested to cause local damage as starting mechanisms of some NDDs [348]. A leaky BBB, fibrinogen infiltration and microglial activity may cause neuronal damage in ‘inflamed’ AD brain [461].

Activated microglia may be both neurotoxic and neuroprotective, depending on several factors including aging, but the causes for transformation between the two actions remains largely unknown [355]. Microglia form the brain’s innate immune cell type, but also are associated with constant phagocytotic clearance of cell debris, representing an essential link between degeneration and regeneration. Insufficient clearance by microglia, present in several NDDs and declining with aging, is associated with an inadequate regenerative response [356], while astrocytes produce anti-inflammatory and neuroprotective agents [357].

Components related to AD neuroinflammation include microglia and astrocytes, the classic and alternate pathways of the complement system, the pentraxins, acute-phase proteins, neuronal-type nicotinic acetylcholine receptors, peroxisomal proliferation-activated receptors, as well as ‘pro-inflammatory’ cytokines and chemokines. In animal models and human brains, both the microglia and astrocytes may generate $\text{A}\beta$, which itself may act as a pro-inflammatory agent inducing the activation of glia and many inflammatory components [358]. The patterns of cytochemokine involvement strengthen the inflammatory theory of AD and raise a pathophysiological role for selective alteration of this network [359]. Footprints of radicals and peroxynitrite attack have been detected in post-mortem AD brain, which, at least in part, are produced by activated microglia, and, together with anomalous release of cytokines and chemokines, but also systemic inflammation with increase in serum $\text{TNF}\alpha$, may be a progression factor in AD [350, 360, 361]. In both aged and AD brain and in animal models, deposition of $\text{A}\beta$ is likely to trigger inflammatory cascades with increased production of pro-inflammatory factors, part of which are localized in the $\text{A}\beta$ plaques and in the surrounding activated glia [355]. Inflammation potentially increases brain levels of $\text{A}\beta$ by three mechanisms: increased influx, decreased efflux, and increased neuronal production [362]. JNK-AP1 signalling pathway may be responsible for $\text{A}\beta$ -induced neuroinflammation in cultured human brain endothelial cells and AD brain and this signalling pathway may serve as a therapeutic target for relieving $\text{A}\beta$ -induced inflammation [363], and $\text{TNF}\alpha$ gene polymorphism may affect the risk of developing AD [364]. $\text{A}\beta$ oligomers and fibrils stimulate differential activation of microglia [358]. Inactivation of pro-inflammatory cytokines such as TNF, despite known adverse effects, makes it an attractive target for therapeutic development to treat NDDs [365]. Inhibiting p53 pathways in microglia alternates microglial

evolved neurotoxicity following exposure to Alzheimer peptides [462]. The problems of AD and tg animal models treated by immunotherapy causing plaque removal and increase in severity of cerebral amyloid angiopathy, but not preventing progressive ND, are not discussed here [see 366–368].

On the other hand, in human AD brain deposits of A β devoid of τ^+ structures were found to be co-localized with non-activated, ramified dystrophic microglia suggesting that A β does not trigger microglial activation [369]. These findings and recent experimental evidence [370] argue against the hypothesis that neuroinflammatory changes contribute to AD. They support the idea that progressive, age-related microglial degeneration and loss of microglial neuroprotection rather than induction of microglial activation contribute to the onset of sporadic AD [369].

In PD, SN cell degeneration is accompanied by astroglial reaction and proliferation of MHC class II positive microglia releasing pro-inflammatory cytokines, nitric oxide, complements, and OS that may be both inducing factors or sequelae of neuronal death [371, 463]. The pattern of humoral immune reactivity is consistent with activation of microglia leading to the targeting of DA nigral neurons for the destruction in both idiopathic and genetic cases of PD [372]. Parkin deficiency increases vulnerability to inflammation-related nigral degeneration, while human neuromelanin induces neuroinflammation and degeneration in the rat SN [373], and aggregated α Syn activates microglia. DA cell death is probably influenced by the innate immune system, and in an MPTP mouse model T cell-mediated DAergic toxicity is almost exclusively arbitrated by CD4 $^+$ T cells and requires the Fas/FasL but not the IFN γ cytotoxic pathway [374]. Intrastratial lipopolysaccharide injection served as a model for inflammatory-induced mitochondrial dysfunction causing NDD in the nigrostriatal system [375]. Microglial activation and corresponding DAergic terminal loss in early PD support the notion that neuroinflammatory responses by intrinsic microglia contribute to the progressive degeneration in PD and related diseases [376]. Part of the specific vulnerability of the SN could be a consequence of h-TNF α hypomethylation [377], TNF α overexpression inducing apoptosis of neuronal cells. On the other hand, microglia may be affected by the disease process and may therefore not be capable of exerting sufficient neuroprotective function, such as glutathione peroxidase expression [241].

Microglia activation in HD has been shown to correlate with severity of the disease [378], with a close spatial and temporal relationship to neuronal dysfunction, and has already been detected in presymptomatic HD gene carriers [379]. BDNF and its receptor levels have been assessed in human cortices affected by HD [347]. Alterations of the adaptive immune system in sALS suggest early involvement of a 'neuroinflammatory' process in the pathobiology of ALS [350, 380]. The role of inflammation in tg models of NDDs, in particular in mouse models of AD, have been reviewed recently [381]. In conclusion, whereas recent studies provide evidence for microglial abnormalities in several NDDs including ALS, HD and Creutzfeldt-Jakob disease [382, 383], the involvement of microglia in the pathogenesis of AD and PD remains controversial [369, 384].

The final pathway: multifaceted neuronal death

Neurons undergo diverse forms of cell death depending on the nature and severity of the stress. The nature, time course and molecular causes of cell death in NDDs and their relations to basic processes are still a matter of discussion [see 1]. Based on distinct morphologic criteria and biochemical features, PCD is classified into three major types: apoptosis (PCD type I), autophagy (PCD type II) and oncotic necrosis, a passive killing of the cell (PCD type III) [385–387]. Morphologically, apoptosis, dependent on caspase activation, is characterized by chromatin condensation (pyknosis), nuclear fragmentation, cell shrinkage and plasma membrane blebbing. The cell breaks into small membrane-surrounded fragments (apoptotic bodies), which are cleared by phagocytosis *in vivo* without inciting an inflammatory response, phagocytotic activity being balanced by positive and negative signals. Apoptosis can occur locally, without damaging healthy adjacent cells. This is in contrast to necrosis, an accidental and uncontrolled mode of cell death (PCD type III, not dependent on caspase activation), but triggered by OS [388], which exhibits rapid cell swelling and subsequent rupture of the plasma membrane that, due to an inflammatory response, usually induces substantial secondary cell damage in the surrounding tissue [389]. Autophagy (PCD type II), known as the process by which molecules and organelles undergo lysosomal clearance/degradation in order to help maintain cellular homeostasis [160], also depends on caspase activation and a number of autophagy-related proteins and genes such as LC3 (light chain 3) and beclin-1 [171, 172]. Hundreds of caspase substrates have been described but only for a few of them the function of their cleavage by caspase is well understood in the pathogenesis of NDDs [390]. There are many reasons and ways for a neuron to die, among which apoptosis is a specific form that is processed in two major signalling pathways, the extrinsic (death receptor) pathway and the intrinsic (mitochondria based) pathways, with several avenues of cross-talk between them (Fig. 5).

Many of the morphological differences between apoptotic and necrotic processes are thought to be a consequence of the action of cysteine proteases, while caspase and calpain functions in cell death are bridging the gap between apoptosis and necrosis. However, caspase-independent cell death also exists [388]. Tissue-specific impairment of autophagy in CNS tissue causes massive loss of neurons resulting in ND. Autophagic cell death, more correctly cell death with autophagy rather than by autophagy [391], probably represents a failure of neuroprotective mechanisms [392]. The prominence of autophagy in neurons contributing to the build-up of dysfunctional mitochondria and protein aggregates may lead to neuronal cell death, either due to an insufficient autophagic process or to up-regulation of autophagy [391]; both indicating a cross-talk between autophagy and the apoptotic pathways. Although markers for autophagy have been identified in different NDDs [393], it is not yet possible to be certain that these are indicative of the occurrence of autophagic cell death.

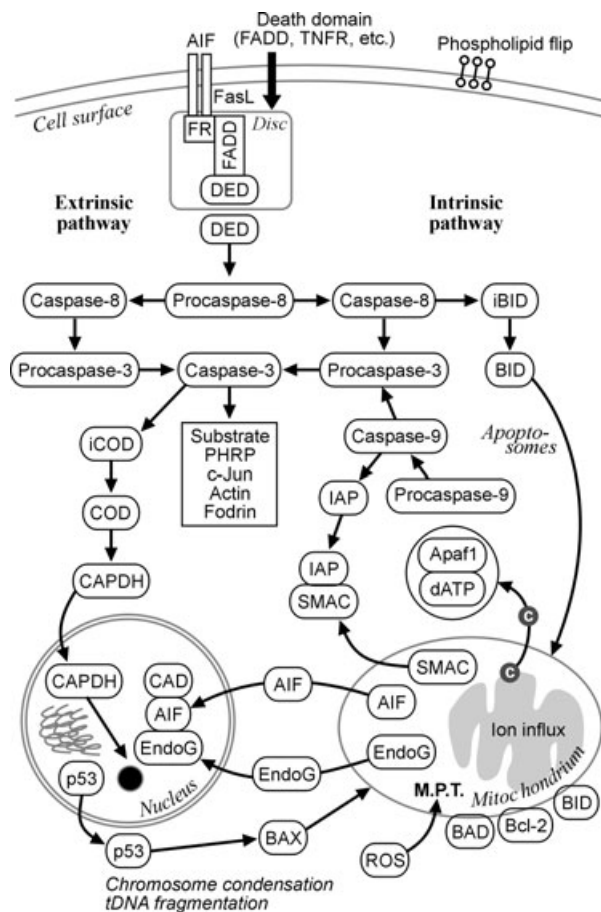


Fig. 5 Overview of apoptotic signalling through the receptor-mediated ('extrinsic') and mitochondria bases ('intrinsic') pathways, showing all key molecular players of apoptosis, the importance of the caspase cascade *via* interaction with different death domains, and the role of effective caspase driving the execution of the cell death program.

Neuronal cell death may exhibit morphologic features of autophagy or necrosis, which differs from that of canonical apoptosis, or autophagic vacuolation can precede apoptotic cell death; this argues against the clear distinction between apoptotic and autophagic cell death [394]. Recent data point to the existence of multiple non-apoptotic, regulated cell death mechanisms, *e.g.* in tauopathies [101], some of which overlap or are mutually exclusive with apoptosis. Increasing evidence suggests that the regulation of neuronal cell death is complex, utilizing multiple pathways that are dependent on the damaging insult [395], each demonstrating specificity of function, regulation and pathway involvement, influenced by subtle differences among cell phenotypes (see Fig. 6).

Whilst post-mortem human brain tissue or those from animal models of injury or disease provide clues as to the diversity of neuronal death, the clearest information about molecular mecha-

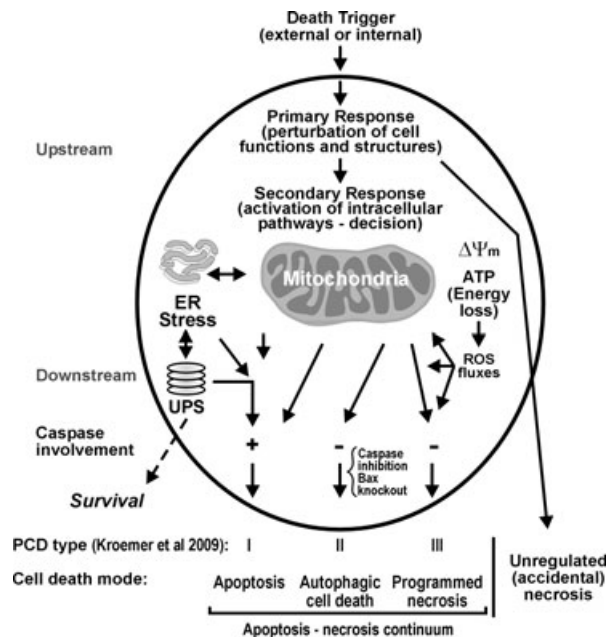


Fig. 6 Diverse pathways leading to cell death, illustrated by the concept of the apoptosis-necrosis continuum that integrates the various death pathways and subsequent intracellular signalling pathways (ER stress, UPS, ATP loss, etc.) to help explain the complex patterns of neuronal death (mix of PCD-types I, II and /or III) (modified from [245]).

nisms leading to death comes from laboratory studies at the cellular level using cell models of injury or disease. Detailed studies of the molecular cell biology of appropriate cultured primary neurones, or immortalized cells with neuronal properties, have enabled the dissection of cellular responses and death outcome. There is an initial primary response to the trigger that may be external (*e.g.* toxic molecules impinging on the cell) or internal (*e.g.* inappropriate intracellular protein aggregation). The primary distortion of cellular biochemistry and physiology, if not rectified by the cell promptly and effectively, activates signalling pathways, both upstream and downstream of mitochondria, causing a crosstalk of PDC processes [245, 257]. Indeed, dying or dead cells may simultaneously manifest characteristics of more than one type of death pathway.

Cell death cascades in major NDDs

Despite demonstration of DNA fragmentation and up-regulation of pro-apoptotic and cell death regulator proteins, it is still unclear, whether apoptotic or necrotic modes are responsible for cell death in NDDs. It is preceded by the activation of caspases and altered expression of pro-apoptotic members of the Bcl-2 family and

other ARPs. Multiple caspases and elevated caspase mRNAs have been detected in post-mortem tissue from AD brains [396], while others observed no apoptotic morphology in AD [397].

Frequent DNA fragmentation and the 'pro-apoptotic' environment in AD brain indicate increased vulnerability of neurons to metabolic and other noxious factors. Recent data suggest that the interaction between APP and/or A β and the cell death mediators p75 (NTR) (the common NTF receptor) and its interaction with pro-apoptotic ligands cause a selective vulnerability of neurons in the cholinergic forebrain in APP [341]. Caspase-3 has been found to be enriched in post-synaptic densities and increased in AD [398] and activation of caspases by PSEN1 gene and its inhibition by secretase inhibition were reported [399]. In surviving neurons, it can be suggested that viability is, in part, maintained by the lack of distal transmission of the caspase-mediated apoptotic signals. This phenomenon of apoptotic avoidance termed *abortive apoptosis* or *abortosis*, may represent an exit from the caspase-induced death program [400]. That, given the robust survivals of neurons with NFTs [401] and recent evidence that NFTs in experimental models do not directly correlate with neuron loss [402] suggests that affected neurons may be able to withhold NFT formation for a long time before they degenerate. Despite a lack of clear evidence linking τ aggregates to neuronal loss, the presence of a tangle in a neuron is likely to be harmful, leading to changes in axonal transport and loss of synapses [403]. Associations between tangle bearing neurons with caspase activation suggests that tangles are at least markers of neuronal disease [101]. Although considered neuroprotective, like other significant intracellular and neuritic protein aggregations they finally contribute to dysfunction and death of involved neurons.

Recent data indicating a link between the development of A β and NFT/ τ pathologies may be due to caspase activation and cleavage of APP which facilitate production of A β and by cleavage of τ may initiate or accelerate the development of tangle pathology [404, 405]. In several tg τ models, an increased number of TUNEL⁺ neurons and ultrastructural features of both apoptosis and necrosis, but no activated caspases were observed [406], while in aging PS/APP mice a crosstalk between apoptosis and autophagy was identified, which influences neuronal survival in AD-related ND [407]. However, many questions remain open about how changes in τ lead to ND and the relationship of NFT pathology to neuronal death, which recently is proposed to be a non-apoptotic caspase-associated form of death [101].

Cell death is a significant part of the pathology of PD. Although the process is mysterious, the prime suspect for a toxic protein is α Syn and its aberrant forms, including increased expression of the normal gene [408]. Apoptosis may be involved in PD, although the molecular mechanisms that initiate dopaminergic neuron loss are not known. These include, among others, JNK signalling, p53 activation, cell-cycle reactivation and signalling through Bcl-2 proteins [244]. Whether PCD actually occurs within the human PD brain remains controversial, and this possibility has been neither confirmed by numerous studies nor definitely excluded [see 1].

The question whether LBs and other α Syn aggregates are harmful or cytoprotective still remains unresolved. Although their formation may reflect one of several response patterns by the CNS to upstream dysregulation of α Syn metabolism, the α Syn pathway appears to be an essential factor for the selective multisystemic loss of neurons and glia in many synucleinopathies, *e.g.* PD, PDD, DLB, multiple system atrophy (MSA), and related disorders, showing widespread occurrence of LBs and dystrophic neurites with neuronal loss in many regions of the central, peripheral and autonomic nervous system. In sporadic ALS persistent cleavage and nuclear translocation of AIP in motor neurons in the spinal cord have been described recently [409].

A specific issue is whether a particular NDD is cell-autonomous, where neurons form the primary defective entities in isolation from surrounding cells. Additionally, there are also functional changes in glial cells, such as astrocytes, which normally sustain neurones. There is a glutamatergic interplay between neurons and astrocytes, disturbances of which may be involved in neuronal derangement and contribute to disease development [410–412]. Such glial perturbations (non-cell-autonomous) are thought to apply in several NDDs [413]. The heterogeneous astroglial responses in various synucleinopathies, tauopathies and other NDDs indicate distinct underlying pathogenic mechanisms in each disorder [414], while in other diseases, *e.g.* MSA, there is a definite relation between oligodendroglialopathy and neuronal degeneration [415, 416]. While astrocytic dysfunction could play its part in the progression and severity of AD [417], the role of astrocytes in PD, ALS and related disorders is poorly understood [414, 418, 419]. Astrocytes display very different biological profiles when they become 'reactive' and an emergent literature indicates the normal homeostatic or sustenance relationships, are disrupted turning them instead into 'collaborators in neurotoxicity' [see 420, 421].

Post-mortem analysis can bridge some but not all of our knowledge gaps; the results are still controversial, and we need a better understanding of the molecular basis and pathways that drive the yin-yang between neuronal survival and death. The combined use of *in vitro* models and new analytical models should help to map environmental and toxic pathways in the aetiology of NDDs [422]. Understanding neuronal death pathways and their cross-talk not only informs the detailed pathobiology but also suggests novel therapeutic modalities, some of which have been reviewed recently [2, 91, 133, 154, 198, 201, 254, 366, 405, 423]. An extensive discussion of effective prophylactic and treatment strategies appears to be outside the goal of the present review.

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