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# Autophagy and Cell Death in Alzheimer's, Parkinson's and Prion Diseases

*Samo Ribarič and Irina Milisav Ribarič*

## Abstract

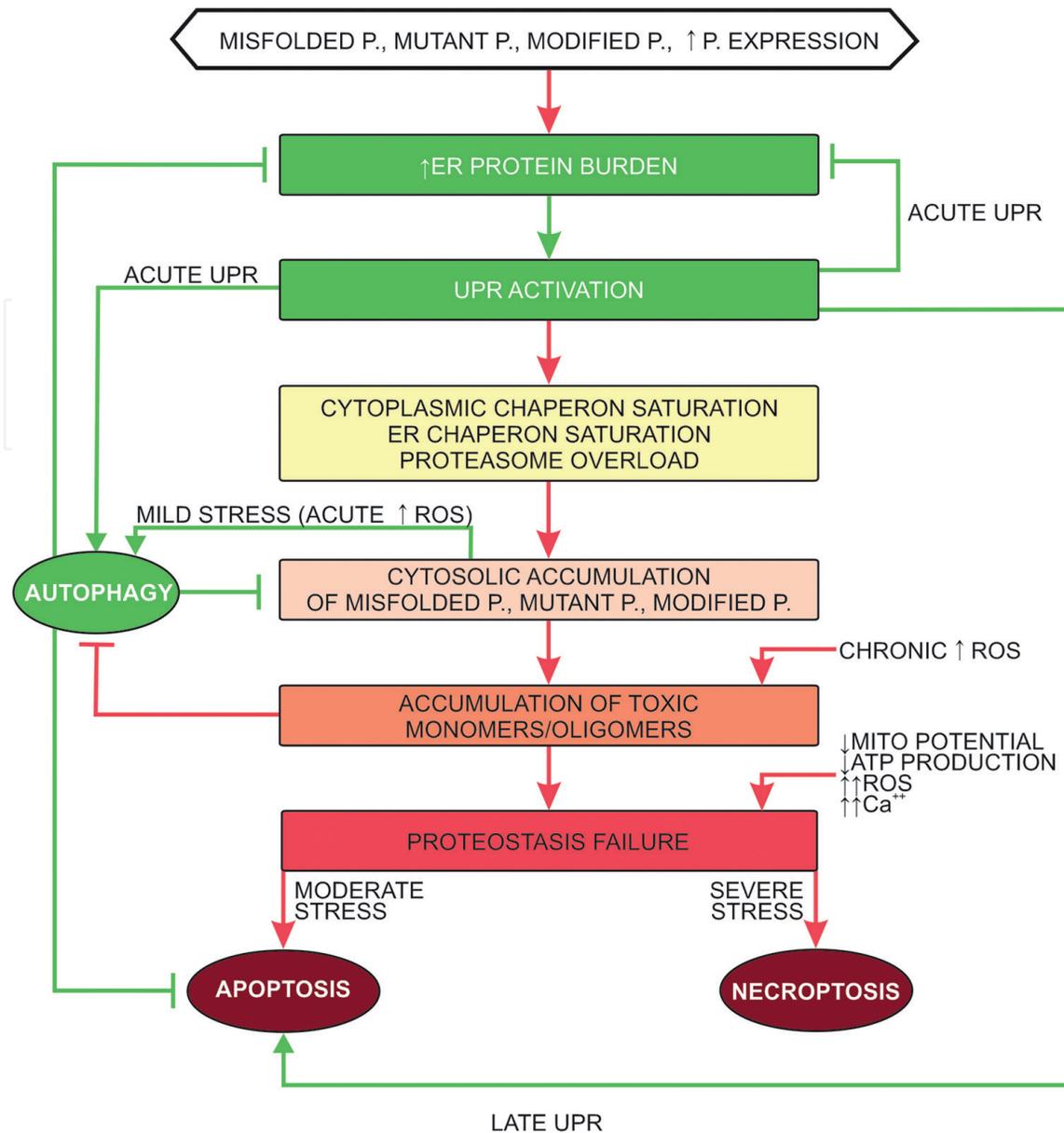
Neurodegenerative brain disorders (NBD) impair brain cells' proteostasis with the accumulation of normal, mutant, misfolded or unfolded proteins in the endoplasmic reticulum (ER). The increased ER burden of these proteins elicits the unfolded protein response (UPR) and stimulates autophagy (AUT). In the short term, UPR and AUT attenuate ER's burden. With prolonged ER stress, the UPR changes from supporting cell survival to promoting apoptosis. The failure of the UPR, to meet the increased protein burden, leads to an increase in cytosolic protein accumulation that initially further stimulates AUT. Over time, the accumulated proteins in the cytosol undergo post-translational changes into toxic monomers and oligomers that repress AUT at multiple levels and promote cell death. This review describes the interlinked signalling pathways of AUT, apoptosis and necroptosis and their modulation by Alzheimer's, Parkinson's and prion diseases and outlines the pharmacological strategies for targeting AUT, apoptosis and necroptosis signalling pathways.

**Keywords:** Alzheimer's disease, apoptosis, autophagy, necroptosis, neurodegenerative brain disorders, Parkinson's disease, prion diseases, proteostasis

## 1. Introduction

### 1.1 Proteostasis in neurodegenerative brain disorders (NBD)

Proteostasis integrates synthesis, folding, trafficking and degradation of proteins. It is perturbed in the early stages of neurodegenerative brain disorders (NBD), before clinical manifestations [1–3]. Mutant, misfolded or unfolded proteins (P) or increased P production increases the endoplasmic reticulum (ER) protein burden in NBD such as Alzheimer's (AD), Parkinson's (PD) and prion diseases (PrD). This increased ER burden stimulates the unfolded protein response (UPR) and autophagy (AUT). The UPR response to ER stress is dichotomous [4–7]. During acute ER stress, UPR supports cell survival, by reducing ER's protein folding load and increasing ER's protein folding capacity. With prolonged ER stress, the UPR preferentially represses cell survival and triggers apoptosis. The failure of ER's stress responses (i.e. increased protein folding capacity and enhanced removal of mutant, misfolded or unfolded proteins by the UPR pathway) to attenuate the P burden leads to an increase in cytosolic P accumulation that further stimulates AUT. Over time, these P undergo post-translational changes and produce toxic monomers and

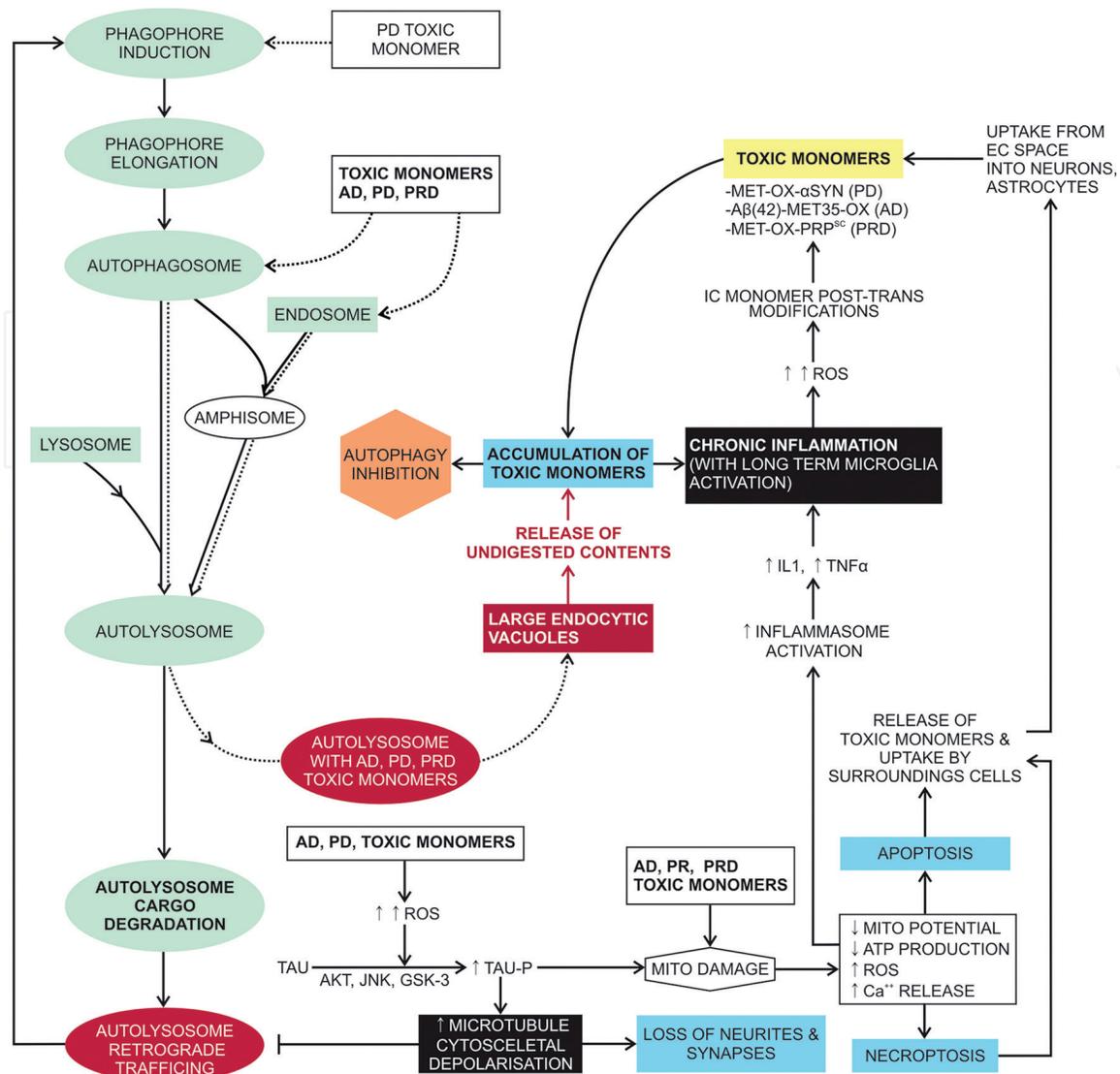


**Figure 1.** Proteostasis in human neurodegenerative brain disorders (NBD). Abbreviations: P (proteins), ER (endoplasmic reticulum), UPR (unfolded protein response), ROS (reactive oxygen species); red lines and arrows indicate progressive failure of proteostasis ultimately leading to NBD. Green arrows and lines indicate appropriate responses of proteostasis to altered P that prevent or slow down the progress of NBD.

oligomers; their production is stimulated by chronic inflammation and increased reactive oxygen species (ROS) production. These monomers and oligomers repress AUT and trigger either apoptosis or necroptosis (**Figure 1**) [4, 6–8].

## 1.2 Autophagy changes in selected NBD

An efficient autophagy (AUT) delays or attenuates the progression of AD, PD and PrD [9–12]. A summary of AUT changes in selected NBD is shown in **Figure 2**. Post-translationally modified proteins (PTMP)—such as soluble amyloid  $\beta$ -peptide 42 with a single oxidised methionine residue at position 35 ( $A\beta_{42}$ -MET35-OX) in Alzheimer’s disease, alpha-synuclein oxidised on methionine residues (MET-OX- $\alpha$ SYN) in Parkinson’s disease and oxidised, self-propagating infectious isoforms of prion protein (MET-OX-PRP<sup>Sc</sup>) in prion diseases (PrD)—inhibit (a) AUT, in AD, PD and PrD, and also (b) mitochondrial (MITO) function [13–23]. MET-OX-PRP<sup>Sc</sup> indirectly damage MITO function. The normal prion protein (PrP<sup>C</sup>) binds with



**Figure 2.** Summary of AUT changes in selected NBD. Abbreviations: AKT (protein kinase B), GSK3 (glycogen synthase kinase 3), JNK (c-Jun N-terminal kinase), TAU (TAU protein), TAU-P (phosphorylated TAU protein).

a variety of molecules, including copper ions [24, 25], and PrP<sup>c</sup> expression levels correlate with Cu/Zn superoxide dismutase, glutathione reductase and cytochrome c oxidase activities [26]. These observations support the hypothesis that PrP<sup>c</sup> is (a) an important endogenous scavenger, protecting structural and signalling proteins from oxidation, due to its high number of methionine residues, and (b) vital for the intracellular transport of copper to superoxide dismutase, which is dependent on copper binding for its antioxidant function. Loss of PrP<sup>c</sup>, due to conversion to PrP<sup>Sc</sup> and MET-OX-PrP<sup>Sc</sup>, which do not bind copper and have a reduced antioxidant activity, reduces the cell's intracellular antioxidant and copper transport capacity and precipitates MITO dysfunction, due to an increased oxidation of cytochrome c oxidase and other MITO proteins [27–30].

AUT is inhibited at the stage of protein digestion (during autolysosome cargo degradation) by the undigestible PTMP and is diverted to the formation of large endocytic vacuoles that rupture and release the undigested PTMP into the cytosol, thus progressively increasing their intracellular concentration. PTMP of AD and PD accelerate microtubule cytoskeletal depolarisation, thus blocking autolysosome retrograde trafficking and accelerating loss of neurites, synapses and synaptic transmission [31–39]. PTMP inhibition of MITO function leads to (a) a reduced ATP production and an increased MITO release of ROS and Ca<sup>2+</sup> into the cytosol [38, 40–44] and

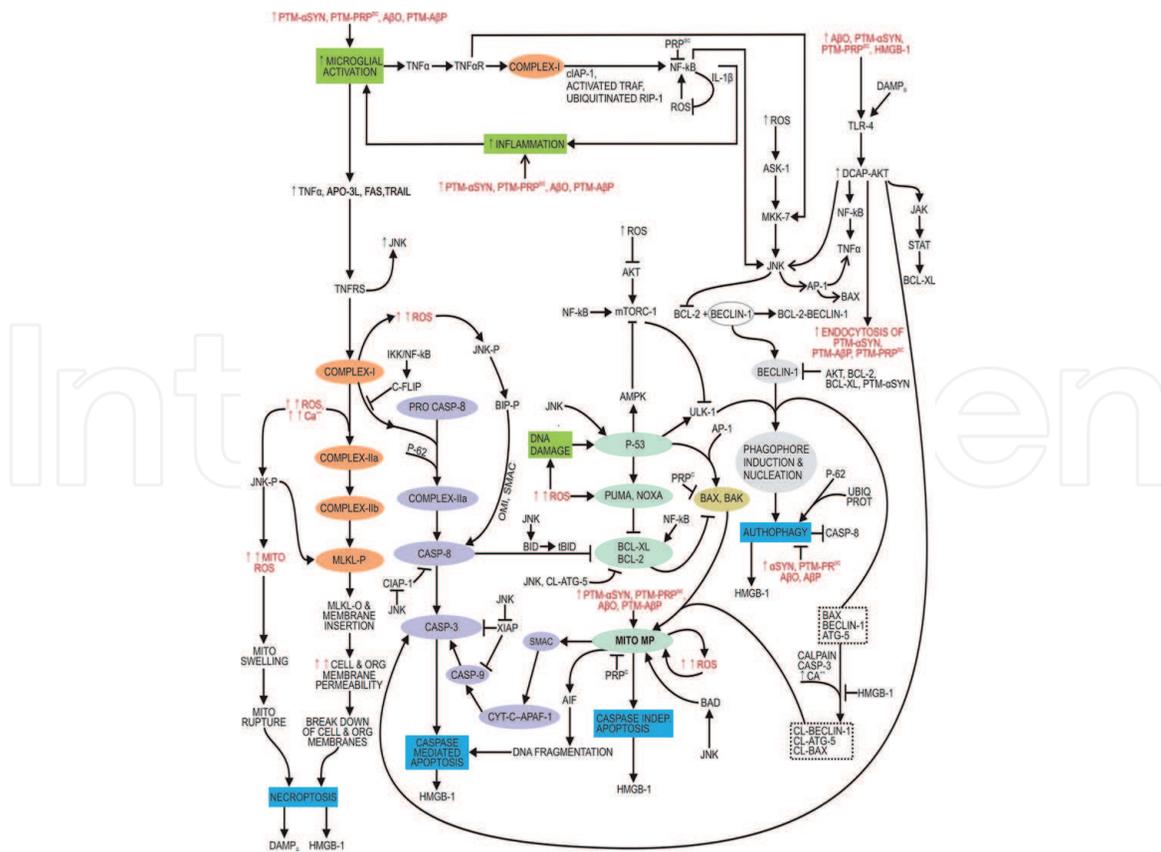
(b) activation of inflammasomes with an increased release of cytokines interleukin 1 (IL1), from microglia, and tumour necrosis factor alpha (TNF $\alpha$ ), from astrocytes and neurons, and finally apoptosis or necroptosis [38, 45–52]. Apoptosis or necroptosis of nerve cells and astrocytes releases PTMP and their oligomers into the extracellular space, thus contributing to the spread of inflammation and neurodegenerative disorder in the brain. The physiological process of apoptosis that normally prevents the spill of cell's molecules to the extracellular space is perturbed by the altered proteostasis into a pathological one in NBD. This transformation is sustained by several intracellular processes including the accumulation of undigestible PTMP, increased oxidative stress, and distorted expression of apoptotic proteins [53–56].

The AUT capacity of brain cells is important in the regulation of immune responses and inflammation that occur in NBD [57, 58]. Protein aggregates (aggresomes), present in age-related NBD, activate inflammasomes. Activated inflammasomes lead to a low-grade inflammation associated with a declined autophagic capacity [59]. On the other hand, autophagy attenuation leads to inflammasome precipitated excessive caspase-1 activation and elevated IL-1 $\beta$  secretion in response to lipopolysaccharide (LPS) stimulation [10, 60, 61]. Also, ER stress and inflammation coexist in NBD, for example, in AD, and are intertwined [57]. Chronic neuroinflammation (CNI) develops into a self-damaging process and is an important factor in sustaining NBD including AD, PD and PrD. CNI includes activation of microglia and astrocytes and infiltration of peripheral immune cells. Transient activation of microglia, accompanied by the release of inflammatory cytokines that amplify the inflammatory response by activating and recruiting astrocytes and peripheral immune cells to the brain lesion, ensures the brain's integrity by removing foreign bodies and cell debris. CNI is toxic to neurons due to sustained release of inflammatory cytokines (e.g. ILs 1 $\beta$  and 6, TNF $\alpha$ ) and ROS and microglial phagocytosis of neighbouring intact nerve cells, thus contributing to the development and progression of NBD. The progressive loss of neurons further contributes to generation of cell debris and sustains microglial hyperactivation [62].

The detrimental effects of PTMP, sustained inflammation and increased ROS production are further exacerbated by the formation of AUT-resistant soluble A $\beta$  oligomers (A $\beta$ O) in AD and AUT-resistant  $\alpha$ SYN oligomers in PD that further stimulate chronic inflammation and increased cytosolic ROS, contributing to apoptosis or necroptosis of neurons. Therefore, activation of apoptosis or necroptosis in AD, PD or PrD is triggered by a positive feedback loop between chronic inflammation in the brain (to which astrocytes and microglia are the main contributor) and the production of PTMP. In addition to high levels of ROS, the production of PTMP in the cytosol is facilitated by copper ions in AD [63] and by iron ions, dopamine and accumulation of alpha-synuclein (the precursor of oxidised  $\alpha$ SYN monomer) in PD [17]. Although chronic brain inflammation contributes to the process of PrP<sup>Sc</sup> production, it is not necessary to sustain it, since the PrP<sup>Sc</sup> only needs the PrP<sup>c</sup> molecules for its propagation [64].

## **2. Crosstalk among AUT, apoptosis and necroptosis signalling pathways in selected NBD**

AUT, apoptosis and necroptosis have interlinked signalling pathways. Examples of key signalling molecules that regulate the transition among these three processes are presented in Section 2.1. The crosstalk among AUT, apoptosis and necroptosis signalling pathways, with the potential sites of modulation by Alzheimer's, Parkinson's and prion diseases (PrD), is summarised in **Figure 3**.



**Figure 3.**

Crosstalk among AUT, apoptosis and necroptosis signalling pathways with the potential sites of modulation by AD, PD and PrD. Abbreviations:  $\alpha$ SYN (alpha-synuclein); A $\beta$ O (amyloid  $\beta$  oligomers); A $\beta$ P (amyloid  $\beta$  monomers with 39 to 42 amino acid residues); AIF (apoptosis-inducing factor); AKT (protein kinase B); AMPK (5' AMP-activated protein kinase); AP-1 (activator protein 1); APAF-1 (apoptotic protease activating factor 1); APO-3L (APO3 ligand); ASK-1 (apoptosis signal-regulating kinase 1); ATG-5 (AUT-related 5); BAD (Bcl2-associated agonist of cell death); BAK (Bcl-2 homologous antagonist/killer); BAX (apoptosis regulator BAX); BCL-2 (B-cell lymphoma 2); BCL-XL (B-cell lymphoma-extra large); Beclin-1 (mammalian ortholog of the yeast AUT-related gene 6 (ATG-6)); BID (BH3 interacting domain death agonist); BIP-P (phosphorylated binding immunoglobulin protein); C-FLIP (FADD-like IL-1 $\beta$ -converting enzyme-inhibitory protein); calpain (proteolytic enzyme, a protein belonging to the family of calcium-dependent, non-lysosomal cysteine proteases); CASP-3, CASP-8/10, CASP-9 (caspase-3, caspase-8/10, caspase-9); cIAP-1 (cellular inhibitor of apoptosis protein 1); CL-ATG5 (cleaved AUT-related 5 (ATG5) protein); CL-BAX (cleaved apoptosis regulator BAX); CL-Beclin-1 (cleaved mammalian ortholog of the yeast AUT-related gene 6); Complex-I (TNF $\alpha$  bound to TNF $\alpha$  receptor that is associated with TRADD (tumour necrosis factor receptor type 1-associated death domain protein), RIPK1 (receptor-interacting serine/threonine-protein kinase 1), TRAF2 (TNF receptor-associated factor 2) and cIAP-1/2 (cellular inhibitor of apoptosis protein 1 and 2)); Complex-IIa (pro-caspase-8, RIPK1, FADD (FAS-associated protein with death domain)); Complex-IIb (pro-caspase-8, RIPK1, RIPK3 (receptor-interacting serine/threonine-protein kinase 3), FADD, MLKL (mixed lineage kinase domain-like pseudokinase)); CYT-C (cytochrome c); DAMPs (damage-associated molecular patterns); DCAP-AKT (activation of toll/IL-1R (TIR) domain-containing adaptor proteins (e.g. mal, TRIF, TRIF-related adaptor molecule, IL-1R-associated kinase-1, IL-1R-associated kinase-M, MAPK, TNFR-associated factor 6, toll-interacting protein)); FAS (apoptosis antigen 1); HMGB-1 (high-mobility group box 1 protein); IKK (I $\kappa$ B kinase enzyme complex, part of the upstream NF- $\kappa$ B signal transduction cascade); IL-1 $\beta$  (interleukin-1 beta); JAK (Janus kinase); JNK (c-Jun N-terminal kinase); JNK-P (phosphorylated c-Jun N-terminal kinase); MITO (mitochondrial); MITO MP (mitochondrial membrane permeability); MITO ROS (mitochondrial reactive oxygen species); MKK7 (MAP kinase kinase 7); MLKL-O (MLKL oligomerisation with translocation and insertion into cell's and organelles' membranes with increased permeability); MLKL-P (phosphorylated pseudokinase mixed lineage kinase domain-like protein); mTORC1 (mammalian target of rapamycin complex 1); NF- $\kappa$ B (nuclear factor kappa-light-chain-enhancer of activated B cells protein complex); NOXA (adult T cell leukaemia-derived PMA-responsive); OMI alias HtrA2 (serine protease HTRA2); ORG (cell organelles); p53 (cellular tumour antigen p53); p62 (nucleoporin p62 protein complex associated with the nuclear envelope); PRO CASP 8/10 (pro-caspase-8/10); PRP<sup>C</sup> (normal form of prion protein); PRP<sup>SC</sup> (self-propagating, protease-resistant, infectious isoforms of prion protein); PTM (post-translationally modified); PUMA (p53 upregulated modulator of apoptosis); RIP-1 (receptor-interacting serine/threonine-protein kinase 1); ROS (reactive oxygen species, e.g. peroxides, superoxide, hydroxyl radical or singlet oxygen); SMAC (second mitochondria-derived activator of caspases); STAT (signal transducer and activator of transcription 3/5); tBID (truncated BID protein); TLR-4 (toll-like receptor 4, member of the pattern recognition receptor (PRR) family); TNF $\alpha$  (tumour necrosis factor alpha); TNF $\alpha$ R (tumour necrosis factor alpha receptor); TNFRS (tumour necrosis factor receptor superfamily); TRAF (TNF receptor-associated factor); TRAIL (TNF-related apoptosis-inducing ligand); UBIQ PROT (ubiquitinated proteins); ULK1 (serine/threonine-protein kinase ULK1); XIAP (X-linked inhibitor of apoptosis protein).

## 2.1 Examples of signalling molecules that regulate crosstalk among AUT, apoptosis and necroptosis pathways in selected NBD

Intracellular *adenosine triphosphate* (ATP) promotes either apoptosis or necroptosis in a concentration-dependent manner; high ATP levels promote apoptosis, and low ATP levels promote necroptosis [65, 66]. Therefore, ATP production in the MITO determines the type of cell death. The best understood inflammation- and necroptosis-promoting cytokine that modulates mitochondrial ATP and ROS levels is TNF $\alpha$  [67]. As explained above, PTMP inhibition of MITO function leads to activation of inflammasomes with an increased release of tumour necrosis factor alpha (TNF $\alpha$ ) from astrocytes and neurons [38, 45–52]. The sustained TNF $\alpha$  stimulation in NBD is the result of two mechanisms. (a) The PTMP of AD, PD and PrD are not digested by AUT; they accumulate in affected cells by their release into the cytosol from endolysosomal and autolysosomal compartment together with proteolytic enzymes [68]. (b) The PTMP in PD and PrD spread through the brain by a prion-like mechanism [69, 70]. The sustained TNF $\alpha$  stimulation can lead to over-activation of PARP1, a nuclear DNA repair enzyme that is activated by DNA damage, due to an increased MITO ROS production. PARP1 over-activation precipitates an acute depletion of NAD<sup>+</sup>, inhibition of oxidative phosphorylation with a severe drop in ATP production and a subsequent activation of necroptosis [65, 71–73].

*AUT-related 5* (Atg5) protein stimulates elongation of autophagosome membranes that envelope PTMP into autophagosomes [74–76] and also regulates the balance between AUT and apoptosis [77]. The neurons' cytosolic Ca<sup>2+</sup> is increased in NBD due to the PTMP elicited (a) ER and MITO release of Ca<sup>2+</sup> into the cytosol [4–7, 78] and (b) an increased Ca<sup>2+</sup> entry through the N-methyl-D-aspartate (NMDAR) glutamate receptor and ion channel proteins from the extracellular space [79–81]. Increased cytosolic Ca<sup>2+</sup> promotes calpain-1- and calpain-2-mediated cleavage of ATG5, with a loss of pro-AUT function and concomitant triggering of cytochrome c-/caspase-mediated apoptosis due to the inhibition of Bcl-xL in the MITO by the cleaved ATG5 [82]. The calpain-1- and calpain-2-mediated cleavage of ATG5 is attenuated by decreased levels of cytosolic Ca<sup>2+</sup> [83]. Cytosolic HMGB1 attenuates apoptosis by protecting the AUT proteins beclin 1 and ATG5 from calpain-mediated cleavage during inflammation [84].

*Beclin 1* stimulates AUT [16, 85, 86]; an enhanced AUT has a concomitant anti-apoptotic effect by clearing apoptosis-associated molecules, for example, active caspase-8 [87–89]. Beclin 1 is cleaved by caspases, thus losing its pro-AUT function, and the cleaved beclin 1 (i.e. C-terminal beclin 1 fragment) promotes apoptosis by triggering the release of MITO cytochrome c [90–92].

*B-cell lymphoma 2* (Bcl-2) family of proteins regulate MITO apoptotic pathway and also AUT; for example, Bcl-2 and Bcl-xL inhibit AUT and apoptosis [93, 94]. Bcl-2 and Bcl-xL proteins have an anti-apoptotic effect, whereas Bax, Bad, Bid, Bim, Bmf, PUMA and NOXA promote apoptosis. Calpain-mediated cleavage of Bax, induced by high cytosolic Ca<sup>2+</sup>, mediates apoptosis [82]. The interactions between anti-apoptotic and pro-apoptotic Bcl-2 family members determine the activation of apoptosis [95–104]. Bcl-2 and Bcl-xL associate with beclin 1 and suppress the beclin 1-dependent autophagic activation [105]. This AUT suppression can be abolished by the pro-apoptotic Bcl-2 family proteins (e.g. Bad, Bid) [106]. The inhibition of Bcl-2 on beclin 1 is also attenuated by phosphorylation of Bcl-2 by JNK-1 or Beclin-1 by DAPK1, thus promoting AUT [107, 108]. Increased expression of Bak, Bad, Bcl-2 and Bcl-x was observed in AD [109]. Cytosolic PrPc protects human primary neurons from Bax-mediated apoptosis [110–112]; therefore the PrP<sup>sc</sup>-precipitated reduction should facilitate apoptosis in PrD.

*Caspase-8* activity is changed in NBD. It has been suggested that an increased caspase-8 activity, associated with an increased caspase-3 activity in the same hippocampal tissue sections from patients with AD, contributes to the development of AD in humans. Recently, two caspase-8 variants, with a reduced activity and associated with an increased risk for development of AD in human, were identified. This finding is consistent with the multiple AD-related changes in the human brain, including loss of synaptic plasticity and memory function and increased microglia pro-inflammatory activation [113]. Caspase-8, within the death-inducing complex II, triggers either apoptotic or necroptotic cell death. Activated caspase-8 promotes apoptosis and also inhibits necroptosis by cleaving RIPK1, RIPK3 and CYLD [114–116], thus preventing CYLD-mediated deubiquitylation of RIPK1 and subsequent RIPK1 kinase activation and necroptosis [117]. The association of caspase-8 with pseudo-caspase cFLIP suppresses apoptosis and also necroptosis, since the residual levels of caspase-8 activity are still sufficient to cleave and inactivate RIPK1 and RIPK3 [118].

*c-Jun N-terminal kinase* (JNK) promotes either apoptosis or necroptosis, depending on its upstream signalling pathways. JNK is required for apoptosis of central nervous system neurons [119]. JNK promotes apoptosis by several signalling pathways that were characterised in different cell experimental models. It is unlikely that all of the observed JNK's pro-apoptotic effects are present in all of the cells at the same time [120]. However, it is important to be aware of the JNK's ability to modulate apoptosis at different levels. To summarise, the known pro-apoptotic effects of JNK are: (a) Activated MAP2Ks phosphorylate JNK and phosphorylated JNK translocates to the nucleus and phosphorylates c-Jun [121, 122] that promotes AP-1 expression; AP-1 promotes transcription of pro-apoptotic proteins TNF- $\alpha$ , Fas-L and Bak [123–125]. (b) JNK phosphorylates p53, enhancing the expression of pro-apoptotic genes Bax and PUMA [126–128]; the increased Bax expression and translocation to mitochondria is sufficient to promote MITO outer membrane permeabilization, the consequent release of cytochrome c and caspase-9 and caspase-3 activation [129–133]. (c) JNK phosphorylates 14-3-3-associated Bad, thus promoting its translocation into MITO and subsequent release of cytochrome c [134, 135]. (d) JNK phosphorylates pro-apoptotic proteins Bim and Bmf, and these phosphorylated proteins activate Bax and/or Bak [136–140]. (e) Phosphorylated Bim binds to and inhibits the Bcl2's anti-apoptotic activity, thus increasing the probability of MITO-activated apoptosis [141, 142]. (f) JNK inhibits the anti-apoptotic Bcl2 by phosphorylation, to induce apoptosis [143, 144]. (g) JNK has the ability to promote apoptosis by stimulating the activity of many pro-apoptotic signalling molecules. (h) Activation of TNFRs (e.g. TNFR1, DR3-6) can lead to apoptosis [144, 145]. (i) Activation of DRs and TNF $\alpha$  receptors stimulates JNK activation that promotes apoptosis by increased expression of DRs [146, 147]; increased expression of pro-apoptotic proteins Bak, Bim and Bax [148, 149]; inhibition of anti-apoptotic proteins XIAP (caspase-3, caspase-7 and caspase-9 inhibitor) and cIAP1 (caspase-8 inhibitor) [150, 151]. JNK's role in NBD is best understood in AD; JNK activation is positively correlated with AD progression [152]. Amyloid- $\beta$  protein fragments activate JNK [153, 154]. Also, JNK phosphorylates tau, thus promoting (a) microtubule cytoskeleton breakdown, (b) attenuation of intracellular transport and (c) loss of synaptic terminals [155–166].

*Activation of tumour necrosis factor receptor superfamily* (e.g. TLRs or TNF $\alpha$ R) or DNA damage can trigger necroptosis by activation of the Complex I-IIa-IIb-phosphorylated pseudokinase mixed lineage kinase domain-like protein (MLKL) signalling pathway; the final steps are (a) RIP3-dependent phosphorylation of MITO proteins PGAM5 and Drp-1 (increasing MITO ROS production); (b) insertion of phosphorylated MLKL into the MITO membrane with the cumulative effects

of increased MITO membrane permeability, loss of membrane potential, decreased ATP and increased ROS production [120, 167–169]; and (c) phosphorylated MLKL's translocation to the plasma membrane and activation of  $\text{Ca}^{2+}$  influx through plasma membrane channels with concomitant plasma membrane breakdown [169]. Increased cytosolic ROS production inactivates MAP kinase phosphatase 1, enabling sustained activation of phosphorylated JNK; phosphorylated JNK promotes necroptosis by (a) stimulating MLKL phosphorylation and by (b) promoting cytochrome c release from MITO via activation of BID [170, 171].

*FLICE inhibitory proteins* (FLIPs). Under stress-free conditions, FLIPs (FLICE inhibitory proteins) attenuate LC3's binding with ATG3, thus preventing ATG3-mediated elongation of autophagosomes and AUT. During stress, FLIPs allow for ATG3-LC3 interaction and stimulate AUT. Therefore, FLIPs (e.g. C-FLIP) can inhibit apoptosis and also AUT [172].

The *high-mobility group box protein 1* (HMGB1) is a nuclear protein released by glia and necrotic or hyper-excitatory neurons after inflammasome activation; it activates receptors for advanced glycation end products (RAGE) and the toll-like receptor (TLR) 4 on neurons and microglia [173, 174]. When HMGB1 binds to TLR4 on neurons, it phosphorylates MARCKS via MAP kinases and induces neurite degeneration, present in AD [173]. The disulphide form of HMGB1 potentiates the microglia pro-inflammatory response; therefore, repeated releases of HMGB from damaged nerve cells during chronic neuroinflammation in PD and AD could lead to an exacerbated neuroinflammatory response of microglia [175–177]. HMGB1, in a rat model of AD, caused (a) inhibition of microglial amyloid  $\beta$ -peptide 42 clearance and enhanced amyloid  $\beta$ -peptide 42 neurotoxicity [178] and (b) dysfunction of microglial amyloid  $\beta$ -peptide 40 phagocytosis [179].

The *nuclear factor kappa-light-chain-enhancer of activated B cells protein complex* (NF- $\kappa$ B) signalling pathway was repressed in a prion-infected cell line and animal brain tissues as evidenced by a decreased level of transcription factor p65/nuclear factor NF-kappa-B p65 subunit (p65) and downregulation of phosphoinositide 3-kinase (PI3K) and protein kinase B (PKB/Akt) in both experimental models [180]. In AD cell models, the exposure to amyloid  $\beta$ -peptide or amyloid precursor protein induced NF- $\kappa$ B activation [181, 182], and inhibition of NF- $\kappa$ B transcriptional activity increased neuronal death in the presence of amyloid  $\beta$ -peptide [183]. NF- $\kappa$ B activation can protect neurons against amyloid  $\beta$ -peptide-induced cell death [184]. Patients with PD have an increased percentage of dopaminergic neurons in the substantia nigra with nuclear p65 immunoreactivity [185]. NF- $\kappa$ B is one of the several factors that regulate Beclin-1 expression; Beclin-1 promotes AUT by stimulating autophagosome formation [186–188]. Increased NF- $\kappa$ B activation in the brain, in addition to stimulating AUT, protects nerve cells against NBDs' mediated injury by several mechanisms including increased transcription of MITO antioxidant enzyme manganese superoxide dismutase (MnSOD) and Bcl-xL genes [189].

*Sirtuins* (SIRT1), NAD<sup>+</sup>-dependent protein deacetylases, modulate apoptosis and necroptosis [190]. For example, SIRT1 promotes AUT by deacetylation of ATG5, ATG7 and ATG8 [191]. Following TNF $\alpha$  receptor stimulation, SIRT2 promotes the association of RIP1 and RIP3, the subsequent formation of complex II and necroptosis [192]. In animal and cell culture models of AD, SIRT1 reduces neurodegeneration in mouse hippocampus and promotes primary neuronal survival [193]. The reduced SIRT1 mRNA and protein levels are associated with an accumulation of amyloid  $\beta$ -peptide 42 and tau in the brains of AD patients [194].

*Tumour protein p53* (p53) modulates AUT and apoptosis. It promotes apoptosis by Bax activation in the cytoplasm; BAX initiates apoptosis by triggering mitochondrial cyt c release and caspase-3 activation [195]. In the nucleus, p53 activates transcription of Bax, PUMA and Noxa [196]. PUMA displaces cytoplasmic p53 from

the Bcl-xL-p53 complex, promoting p53 activation of the apoptotic pathway [197]. In the nucleus, p53 also stimulates AUT through transcription activation of ULK1, sestrin1/2 and damage-regulated AUT modulator (DRAM) [198, 199]. Indirectly, p53 promotes AUT by mTOR inhibition, via activation of AMP-dependent kinase and tuberous sclerosis (TSC) 1/TSC2 complex pathway [200]. It was suggested that DRAM has a dual role of promoting either AUT- or p53-mediated apoptosis [201]. In a *Drosophila* model of AD tauopathy, p53 prevented neurodegeneration by increased expression of amphiphysin, clathrin light chain, clathrin heavy chain, RAS oncogene family and synaptotagmin  $\beta$  synaptic genes [202]. p53 levels are significantly increased in brains of patients with AD [203] and are correlated with brain MITO dysfunction [204]. Recently, it was suggested that tau oligomers sequester and downregulate functional phospho-p53 in an AD mouse model and in patients with AD [205].

*Ubiquitin-binding protein p62* (p62) modulates cell death switching between apoptosis and necroptosis. In a cell model, p62 promotes either necroptosis, when p62 is associated with the necrosome (i.e. complex II), or apoptosis when the P62-necrosome association is blocked [206]. The p62 regulates apoptotic and autophagic processes [207]. P62 mediates AUT degradation by first binding polyubiquitinated proteins with the ubiquitin-associated domain and then to autophagosomes through the LC3-interacting region [208, 209]. In response to tumour necrosis factor receptor stimulation, P62 promotes apoptosis by stimulating activation of caspase-8 [210, 211]. The levels of p62 are increased in NBD, for example, in PrD [212, 213]. Autophagy disposal of aberrant proteins is stimulated by the p62-Keap1-NRF2 signalling pathway [214]. For example, in a mouse model of AD, increased brain p62 expression improved cognition by an autophagy-mediated mechanism that reduced amyloid  $\beta$ -peptide 40/42 levels [215].

## **2.2 Summary of similarities/differences in the mechanistic pathways between selected NBD**

Beclin-1, ATG-5, NF- $\kappa$ B, JNK, p53, p62, HMGB1 and ROS are the key signalling molecules that mediate crosstalk among AUT, apoptosis and necroptosis. ATG5 and Beclin-1 in conjunction with ULK-1 and BAX promote AUT by initiating phagophore induction and nucleation steps. Cleavage of ATG-5 and Beclin-1 by calpain, caspase-3 or increased cytosolic free calcium changes their function from stimulating AUT to promoting apoptosis via increased MITO membrane permeability. Cleaved ATG5 inhibits the anti-apoptotic activity of BCL2 and BCL-XL on BAX and BAK, further promoting increased MITO membrane permeability and apoptosis. P53 activation plays a dual role by promoting apoptosis (via activation of PUMA and NOXA) and AUT by ULK1 activation. The JNK signalling kinase blocks the binding of BCL-2 to Beclin-1, thus enabling Beclin-1 to participate in AUT initiation, and also activates the apoptosis-triggering proteins BAX and BAK. Phosphorylated JNK promotes necroptosis by stimulating MLKL phosphorylation and apoptosis by caspase-8 activation. p62 promotes AUT and apoptosis. HMGB-1 is released during AUT, apoptosis and necroptosis, and by inhibiting the cleavage of ATG-5, BAX and Beclin-1 simultaneously promote AUT and inhibit apoptosis. Mild increases in cytosolic ROS act as signalling molecules that promote a physiological balance between AUT, apoptosis and necroptosis, which favour AUT; moderate and high increases in cytosolic ROS concentrations favour apoptosis and necroptosis over AUT. The products of post-translational protein modifications in AD, PD and PrD favour apoptosis and necroptosis over AUT by (a) increasing the activation of apoptosis (e.g. by increasing MITO membrane permeability) and necroptosis, by chronic activation of TLR4 and TNF $\alpha$  receptors [216–234],

(b) promoting moderate to high increases in cytosolic ROS concentrations and (c) attenuating AUT [42, 62, 235–240]. In contrast to PD and AD, PrP<sup>SC</sup>-infected cells are more likely to respond with necroptosis and then apoptosis. For example, a significant upregulation of necroptosis signalling molecules phosphorylated MLKL, MLKL and receptor-interacting serine/threonine-protein kinase 3 (RIP3) was measured in the post-mortem cortical brains of patients with various types of human PRD [241].

### 3. Pharmacological strategies targeting AUT, apoptosis and necroptosis signalling pathways

At present, most of the studies, devoted to the development of pharmacological interventions for NBD, are focused on the crosstalk of AUT and apoptosis signalling pathways in neurons. Future research should also include development of pharmacological interventions that target other cells involved in the development of NBD, including microglia, astrocytes, endothelial cells and pericytes [242]. The development of pharmacological interventions for NBD should be guided by several key questions: (a) How to modulate the role of AUT from pro-death to pro-survival? (b) How is the information from the crosstalk among AUT, apoptosis and necroptosis integrated? (c) How to modulate the crosstalk among AUT, apoptosis and necroptosis? and (d) How is the information from the crosstalk among AUT, apoptosis and necroptosis (e.g. inflammation-promoting molecules) shared among different cells involved in the development of NBD? [242]. Examples of pharmacological strategies are given below:

Pharmacological strategies to ameliorate MITO dysfunction include:

(a) Targeting excessive ROS production:

(a1) Mercaptamine that increases levels of glutathione in human [78].

(a2) Antioxidant vatiquinone used in clinical trials [243].

(a3) RTA-308 stimulates Nrf2 to enhance the expression of pro-oxidant genes and to repress inflammatory genes in an animal model [244].

(a4) Antioxidants coenzyme Q, lipoic acid and green tea polyphenol epigallocatechin gallate attenuate the effects of NBD in animal models [245–248].

(a5) Ceria nanoparticles are ROS scavengers that localise in MITO and suppress neuronal death in an AD mouse model [249].

(b) Targeting mitochondrial biogenesis: stimulation of PGC1- $\alpha$ 's ROS scavenging activity with SIRT1 could attenuate ROS-induced damage in AD [250].

AUT inducers are (a) mTOR inhibitors, either ATP-competitive inhibitors (e.g. Torin1 and related compounds) or non-ATP-competitive inhibitors (e.g., rapamycin and rapalogs), and (b) acting by mTOR-independent targets [238]. The most promising AUT inducers, acting by mTOR inhibition, are the non-ATP-competitive inhibitors rapamycin and rapalogs that are mTORC1 selective and induced AUT in animal models of AD, PD and PrD [251–258]. The AMPK signalling pathway is activated by mTOR-independent AUT activators, for example, by trehalose. Trehalose inhibits GLUT proteins, thus eliciting AMPK activation [259]. Trehalose-induced

AUT induction, with concomitant therapeutic effects, was demonstrated in mouse models of NBD, including AD, PD and PrD [260–265].

TNF $\alpha$  signalling pathway is the focus of pharmacological interventions targeting neuroinflammation in NBD with a variety of compounds [57]: (a) serotonin binds to microglial receptors and has anti-inflammatory effects; serotonin treatment reduced TNF $\alpha$  release in cultured primary microglia cells exposed to A $\beta$ O and in mouse brains infused with A $\beta$ O and also prevented AD-associated behavioural changes [266]; (b) etanercept, a decoy TNF receptor and IgG1 Fc fusion protein that inhibits the binding of soluble TNF to cell-surface TNF receptors, was evaluated in several clinical trials on patients with AD; no statistically significant results were reported; however, the drug was well tolerated, and large-scale trials are expected [57]; and (c) infliximab, a human monoclonal antibody that binds TNF $\alpha$  and was used to treat human auto-immune and inflammatory diseases, prevented eIF2 $\alpha$  phosphorylation and long-term memory loss in a mouse model of AD [7, 267].

#### **4. Conclusions**

Neurodegenerative brain disorders (NBD) change brain cell proteostasis due to the accumulation of normal, mutant, misfolded or unfolded proteins in the endoplasmic reticulum (ER). The increased ER burden elicits the unfolded protein response (UPR) and stimulates AUT. In the short term, these responses tend to attenuate ER's stress, by reducing the ER's protein load and increasing the ER's folding capacity. In the long term, with prolonged ER stress, the UPR changes from supporting cell survival to promoting apoptosis. The failure of the ER stress response to meet the increased protein burden is reflected in an increased cytosolic protein accumulation that initially further stimulates AUT. Over time, the accumulated proteins in the cytosol undergo post-translational changes into toxic monomers and oligomers that repress AUT at multiple levels and promote either apoptosis or necroptosis. Apoptosis and necroptosis of the affected cells lead to the release of toxic proteins into the surrounding tissue and trigger the response of microglia and astrocytes. Chronic neuroinflammation, sustained by the spread of progressive failure of AUT among brain cells, due to the release of toxic monomers and oligomers from dying cells and their uptake by initially healthy cells and by the persistent activation of microglia and astrocytes by toxic monomers and oligomers, also contributes to nerve apoptosis or necroptosis. The signalling pathways of apoptosis, AUT and necroptosis are interlinked. A better understanding on how chronic neuroinflammation, Alzheimer's, Parkinson's and prion diseases modulate the crosstalk among these signalling pathways could contribute to the development of new therapeutic interventions for these NBD.

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#### **Conflicts of interest**

The author declares no conflict of interest.

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