Chapter

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

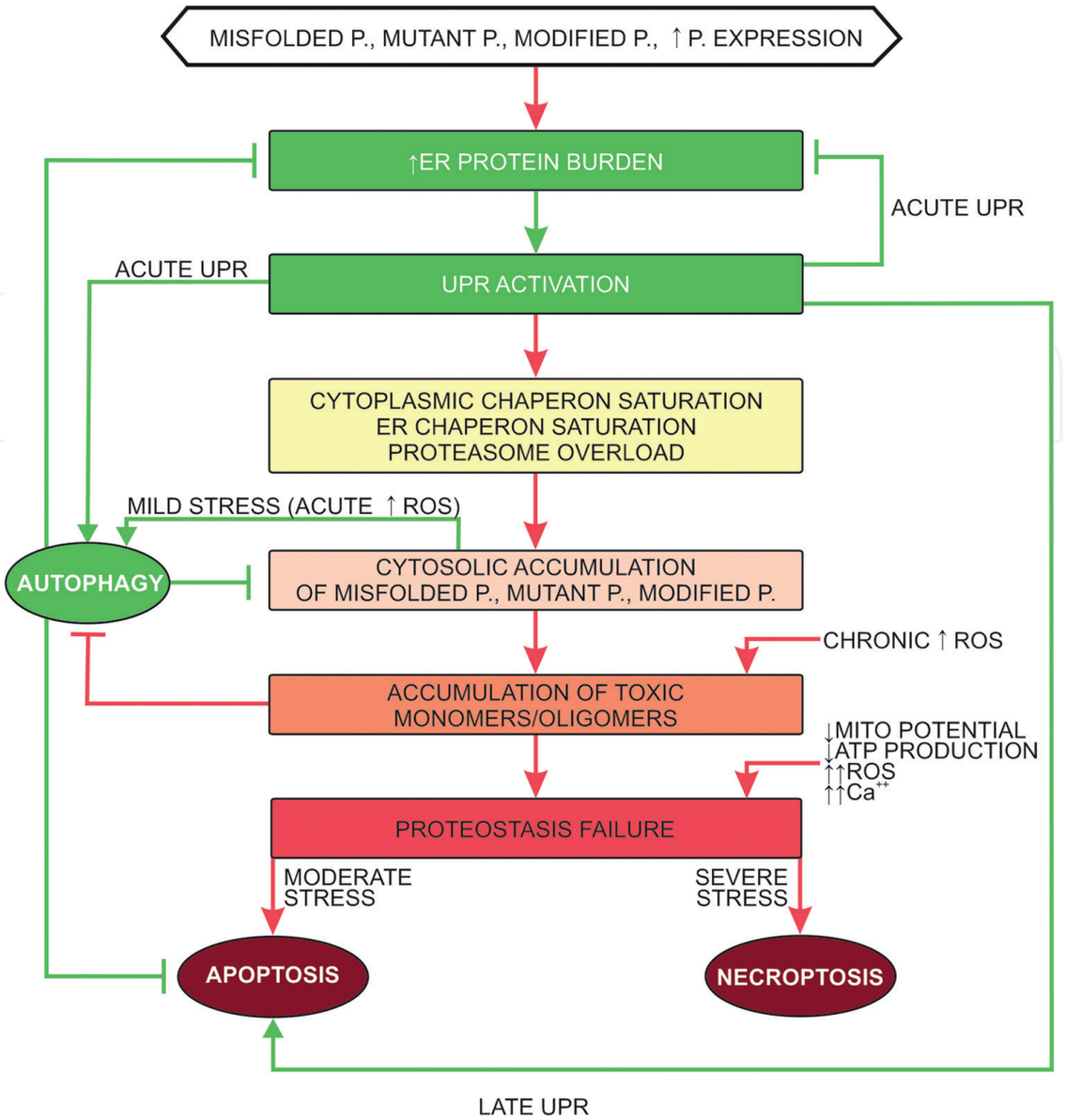

Figure 1.
Proteostasis in human neurodegenerative brain disorders (NBD). Abbreviations: P (proteins), ER (endoplasmic reticulum), UPR (unfolded protein response), ROS (reactive oxygen species); red lines and arrows indicate progressive failure of proteostasis ultimately leading to NBD. Green arrows and 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 β-peptide 42 with a single oxidised methionine residue at position 35 (Aβ42-MET35-OX) in Alzheimer's disease, alpha-synuclein oxidised on methionine residues (MET-OX-αSYN) in Parkinson's disease and oxidised, self-propagating infectious isoforms of prion protein (MET-OX-PRP^{Sc}) in prion diseases (PrD)—inhibit (a) AUT, in AD, PD and PrD, and also (b) mitochondrial (MITO) function [13–23]. MET-OX-PRP^{Sc} indirectly damage MITO function. The normal prion protein (PrP^{c}) binds with

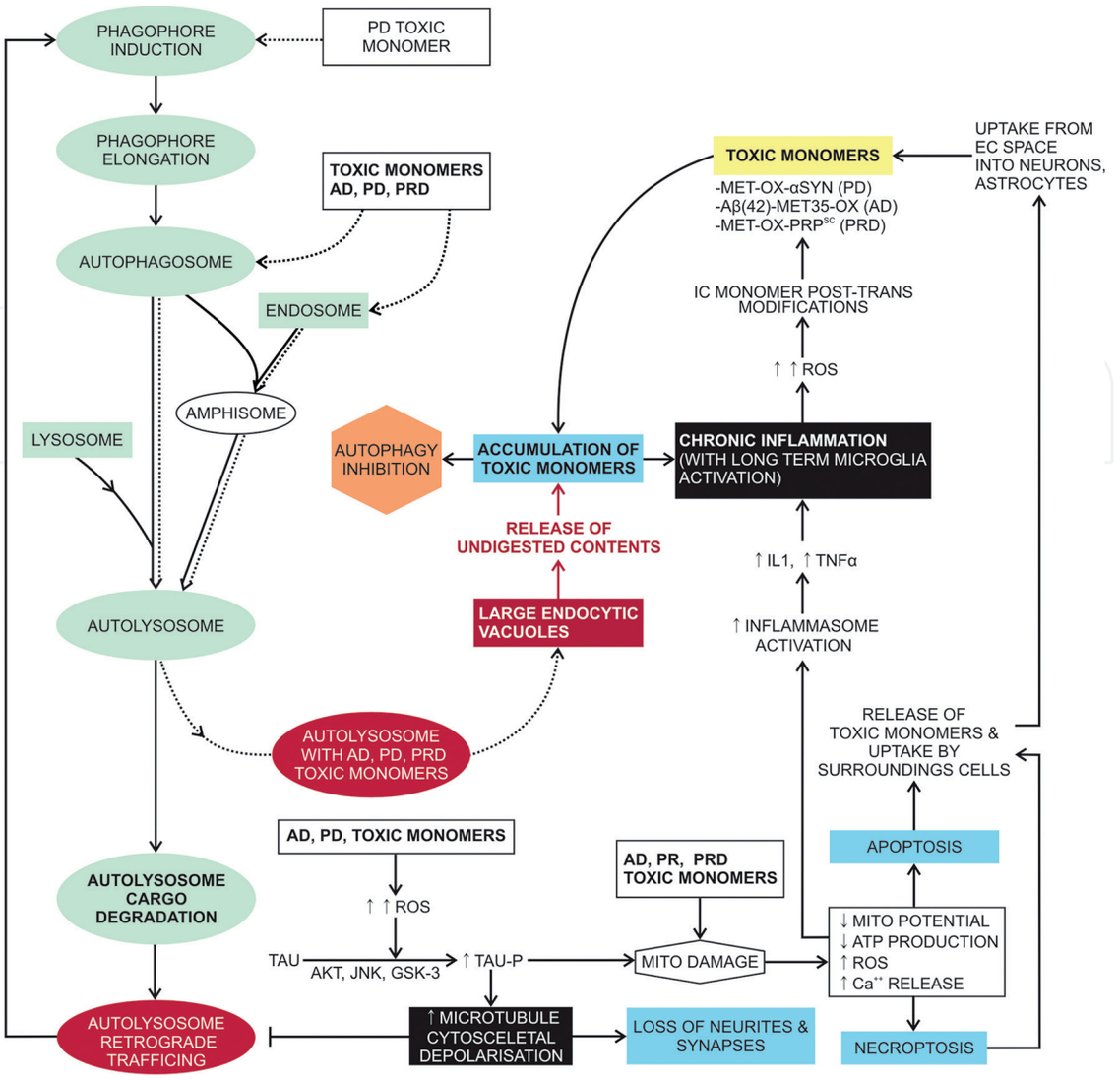

Figure 2.
Summary of AUT changes in selected NBD. Abbreviations: AKT (protein kinase B), GSK3 (glycogen synthase kinase 3), JNK (c-Jun N-terminal kinase), TAU (TAU protein), TAU-P (phosphorylated TAU protein).

a variety of molecules, including copper ions [24, 25], and PrP^{c} expression levels correlate with Cu/Zn superoxide dismutase, glutathione reductase and cytochrome c oxidase activities [26]. These observations support the hypothesis that PrP^{c} 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^{c}, due to conversion to PrP^{Sc} and MET-OX-PrP^{Sc}, 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 microtube 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^{2+} 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 (TNFα), 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-1β 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 1β and 6, TNFα) 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 Aβ oligomers (AβO) in AD and AUT-resistant αSYN 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 αSYN monomer) in PD [17]. Although chronic brain inflammation contributes to the process of PrP^{Sc} production, it is not necessary to sustain it, since the PrP^{Sc} only needs the PrP^{c} 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**.

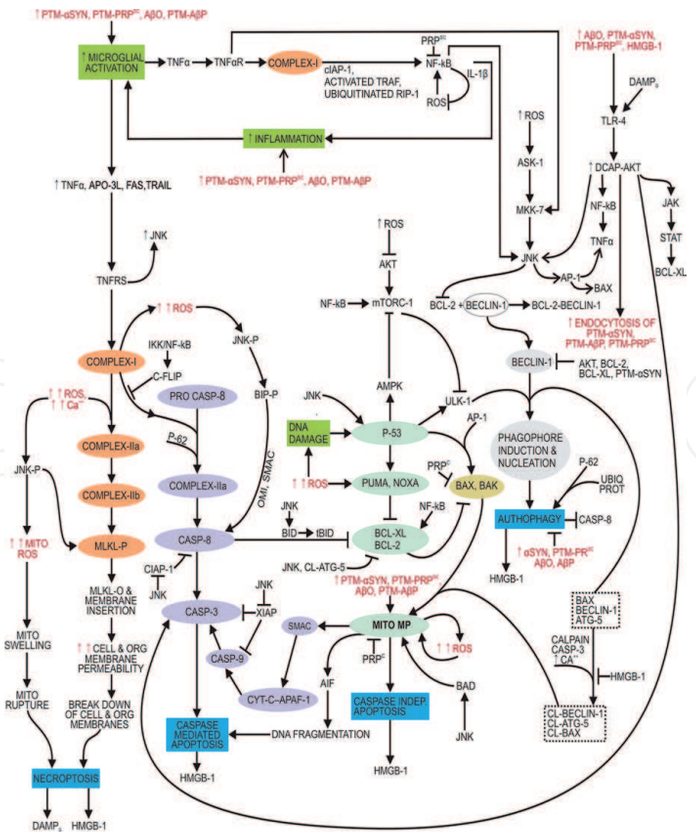

Figure 3.

Crosstalk among AUT, apoptosis and necroptosis signalling pathways with the potential sites of modulation by AD, PD and PrD. Abbreviations: αSYN (alpha-synuclein); AβO (amyloid β oligomers); AβP (amyloid β 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-1β-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 (TNFα bound to TNFα 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 (IκB kinase enzyme complex, part of the upstream NF-κB signal transduction cascade); IL-1β (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-κB (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^{C} (normal form of prion protein); PRP^{SC} (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); TNFα (tumour necrosis factor alpha); TNFαR (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 TNFα [67]. As explained above, PTMP inhibition of MITO function leads to activation of inflammasomes with an increased release of tumour necrosis factor alpha (TNFα) from astrocytes and neurons [38, 45–52]. The sustained TNFα 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 TNFα 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^+, 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^{2+} is increased in NBD due to the PTMP elicited (a) ER and MITO release of Ca^2 into the cytosol [4–7, 78] and (b) an increased Ca^{2+} entry through the N-methyl-D-aspartate (NMDAR) glutamate receptor and ion channel proteins from the extracellular space [79–81]. Increased cytosolic Ca^{2+} 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^{2+} [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 Ca2+, 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 supress 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^{sc}-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-α, 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 TNFα 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-β 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 TNFαR) 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 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 β-peptide 42 clearance and enhanced amyloid β-peptide 42 neurotoxicity [178] and (b) dysfunction of microglial amyloid β-peptide 40 phagocytosis [179].

The *nuclear factor kappa-light-chain-enhancer of activated B cells protein complex* (NF-κB) 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 β-peptide or amyloid precursor protein induced NF-κB activation [181, 182], and inhibition of NF-κB transcriptional activity increased neuronal death in the presence of amyloid β-peptide [183]. NF-κB activation can protect neurons against amyloid β-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-κB is one of the several factors that regulate Beclin-1 expression; Beclin-1 promotes AUT by stimulating autophagosome formation [186–188]. Increased NF-κB 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 (SIRTs), NAD^+-dependent protein deacetylases, modulate apoptosis and necroptosis [190]. For example, SIRT1 promotes AUT by deacetylation of ATG5, ATG7 and ATG8 [191]. Following TNFα 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 β-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 β 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 β-peptide 40/42 levels [215].

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

Beclin-1, ATG-5, NF-κB, 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 TRL4 and TNFα 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^{SC}-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-α'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].

TNFα 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 TNFα release in cultured primary microglia cells exposed to AβO and in mouse brains infused with AβO 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 TNFα and was used to treat human auto-immune and inflammatory diseases, prevented eIF2a 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.

Acknowledgements

The author thanks Professor Irina Milisav for reviewing the manuscript and suggesting improvements. The assistance of Ms. Vanja Mavrin in drawing the final figures is acknowledged.

Conflicts of interest

The author declares no conflict of interest.

Funding

This work was supported by ARRS grant number P3-0171.

Author details

Samo Ribarič* and Irina Milisav Ribarič
Faculty of Medicine, Institute of Pathophysiology, University of Ljubljana, Ljubljana, Slovenia

*Address all correspondence to: samo.ribaric@mf.uni-lj.si

References

[1] Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. Cold Spring Harbor Perspectives in Medicine. 2011;**1**(1):a006189. DOI: 10.1101/cshperspect.a006189

[2] Dickson DW. Parkinson's disease and parkinsonism: Neuropathology. Cold Spring Harbor Perspectives in Medicine. 2012;**2**(8):1-15. DOI: 10.1101/cshperspect.a009258

[3] Soto C, Satani N. The intricate mechanisms of neurodegeneration in prion diseases. Trends in Molecular Medicine. 2011;**17**(1):14-24. DOI: 10.1016/j.molmed.2010.09.001

[4] Martin-Jimenez CA, Garcia-Vega A, Cabezas R, Aliev G, Echeverria V, Gonzalez J, et al. Astrocytes and endoplasmic reticulum stress: A bridge between obesity and neurodegenerative diseases. Progress in Neurobiology. 2017;**158**:45-68. DOI: 10.1016/j.pneurobio.2017.08.001

[5] Gerakis Y, Hetz C. A decay of the adaptive capacity of the unfolded protein response exacerbates Alzheimer's disease. Neurobiology of Aging. 2018;**63**:162-164. DOI: 10.1016/j.neurobiolaging.2017.09.012

[6] Gerakis Y, Hetz C. Emerging roles of ER stress in the etiology and pathogenesis of Alzheimer's disease. The FEBS Journal. 2018;**285**(6):995-1011. DOI: 10.1111/febs.14332

[7] Freeman OJ, Mallucci GR. The UPR and synaptic dysfunction in neurodegeneration. Brain Research. 2016;**1648**(Pt B):530-537. DOI: 10.1016/j.brainres.2016.03.029

[8] Shah SZA, Zhao D, Hussain T, Yang L. The role of unfolded protein response and mitogen-activated protein kinase signaling in neurodegenerative diseases with special focus on prion diseases. Frontiers in Aging Neuroscience. 2017;**9**:120. DOI: 10.3389/fnagi.2017.00120

[9] Bingol B. Autophagy and lysosomal pathways in nervous system disorders. Molecular and Cellular Neurosciences. 2018;**91**:167-208. DOI: 10.1016/j.mcn.2018.04.009

[10] Lai M, Yao H, Shah SZA, Wu W, Wang D, Zhao Y, et al. The NLRP3-caspase 1 inflammasome negatively regulates autophagy via TLR4-TRIF in prion peptide-infected microglia. Frontiers in Aging Neuroscience. 2018;**10**:116. DOI: 10.3389/fnagi.2018.00116

[11] Fan XY, Tian C, Wang H, Xu Y, Ren K, Zhang BY, et al. Activation of the AMPK-ULK1 pathway plays an important role in autophagy during prion infection. Scientific Reports. 2015;**5**:14728. DOI: 10.1038/srep14728

[12] Wang H, Tian C, Sun J, Chen LN, Lv Y, Yang XD, et al. Overexpression of PLK3 mediates the degradation of abnormal prion proteins dependent on chaperone-mediated autophagy. Molecular Neurobiology. 2017;**54**(6):4401-4413. DOI: 10.1007/s12035-016-9985-0

[13] Grant CM. Sup35 methionine oxidation is a trigger for de novo [PSI(+)] prion formation. Prion. 2015;**9**(4):257-265. DOI: 10.1080/19336896.2015.1065372

[14] Nixon RA. Autophagy, amyloidogenesis and Alzheimer disease. Journal of Cell Science. 2007;**120**(Pt 23):4081-4091. DOI: 10.1242/jcs.019265

[15] Pickford F, Masliah E, Britschgi M, Lucin K, Narasimhan R, Jaeger PA, et al. The autophagy-related protein beclin 1 shows reduced expression in early Alzheimer disease and regulates

amyloid beta accumulation in mice. The Journal of Clinical Investigation. 2008;**118**(6):2190-2199. DOI: 10.1172/JCI33585

[16] Salminen A, Kaarniranta K, Kauppinen A, Ojala J, Haapasalo A, Soininen H, et al. Impaired autophagy and APP processing in Alzheimer's disease: The potential role of Beclin 1 interactome. Progress in Neurobiology. 2013;**106-107**:33-54. DOI: 10.1016/j.pneurobio.2013.06.002

[17] Hokenson MJ, Uversky VN, Goers J, Yamin G, Munishkina LA, Fink AL. Role of individual methionines in the fibrillation of methionine-oxidized alpha-synuclein. Biochemistry. 2004;**43**(15):4621-4633. DOI: 10.1021/bi049979h

[18] Leong SL, Pham CL, Galatis D, Fodero-Tavoletti MT, Perez K, Hill AF, et al. Formation of dopamine-mediated alpha-synuclein-soluble oligomers requires methionine oxidation. Free Radical Biology & Medicine. 2009;**46**(10):1328-1337. DOI: 10.1016/j.freeradbiomed.2009.02.009

[19] Elmallah MI, Borgmeyer U, Betzel C, Redecke L. Impact of methionine oxidation as an initial event on the pathway of human prion protein conversion. Prion. 2013;**7**(5):404-411. DOI: 10.4161/pri.26745

[20] Younan ND, Nadal RC, Davies P, Brown DR, Viles JH. Methionine oxidation perturbs the structural core of the prion protein and suggests a generic misfolding pathway. The Journal of Biological Chemistry. 2012;**287**(34):28263-28275. DOI: 10.1074/jbc.M112.354779

[21] Coskun P, Wyrembak J, Schriner SE, Chen HW, Marciniack C, Laferla F, et al. A mitochondrial etiology of Alzheimer and Parkinson disease. Biochimica et Biophysica Acta. 2012;**1820**(5):553-564. DOI: 10.1016/j.bbagen.2011.08.008

[22] Borger E, Aitken L, Muirhead KE, Allen ZE, Ainge JA, Conway SJ, et al. Mitochondrial beta-amyloid in Alzheimer's disease. Biochemical Society Transactions. 2011;**39**(4):868-873. DOI: 10.1042/BST0390868

[23] Siskova Z, Mahad DJ, Pudney C, Campbell G, Cadogan M, Asuni A, et al. Morphological and functional abnormalities in mitochondria associated with synaptic degeneration in prion disease. The American Journal of Pathology. 2010;**177**(3):1411-1421. DOI: 10.2353/ajpath.2010.091037

[24] Brown DR, Qin K, Herms JW, Madlung A, Manson J, Strome R, et al. The cellular prion protein binds copper in vivo. Nature. 1997;**390**(6661):684-687. DOI: 10.1038/37783

[25] Jones CE, Abdelraheim SR, Brown DR, Viles JH. Preferential Cu^{2+} coordination by His96 and His111 induces beta-sheet formation in the unstructured amyloidogenic region of the prion protein. The Journal of Biological Chemistry. 2004;**279**(31):32018-32027. DOI: 10.1074/jbc.M403467200

[26] Zeng L, Zou W, Wang G. Cellular prion protein (PrP(C)) and its role in stress responses. International Journal of Clinical and Experimental Medicine. 2015;**8**(5):8042-8050

[27] Thackray AM, Knight R, Haswell SJ, Bujdoso R, Brown DR. Metal imbalance and compromised antioxidant function are early changes in prion disease. The Biochemical Journal. 2002;**362**(Pt 1):253-258

[28] Brown DR. Neurodegeneration and oxidative stress: Prion disease results from loss of antioxidant defence. Folia Neuropathologica. 2005;**43**(4):229-243

[29] Milhavet O, Lehmann S. Oxidative stress and the prion protein in transmissible spongiform

encephalopathies. Brain Research Brain Research Reviews. 2002;**38**(3):328-339

[30] Nadal RC, Abdelraheim SR, Brazier MW, Rigby SE, Brown DR, Viles JH. Prion protein does not redox-silence Cu^{2+}, but is a sacrificial quencher of hydroxyl radicals. Free Radical Biology & Medicine. 2007;**42**(1):79-89. DOI: 10.1016/j.freeradbiomed.2006.09.019

[31] Alim MA, Hossain MS, Arima K, Takeda K, Izumiyama Y, Nakamura M, et al. Tubulin seeds alpha-synuclein fibril formation. The Journal of Biological Chemistry. 2002;**277**(3): 2112-2117. DOI: 10.1074/jbc.M102981200

[32] Esteves AR, Arduino DM, Swerdlow RH, Oliveira CR, Cardoso SM. Microtubule depolymerization potentiates alpha-synuclein oligomerization. Frontiers in Aging Neuroscience. 2010;**1**:5. DOI: 10.3389/neuro.24.005.2009

[33] Kim M, Jung W, Lee IH, Bhak G, Paik SR, Hahn JS. Impairment of microtubule system increases alpha-synuclein aggregation and toxicity. Biochemical and Biophysical Research Communications. 2008;**365**(4):628-635. DOI: 10.1016/j.bbrc.2007.11.020

[34] Lee HJ, Khoshaghideh F, Lee S, Lee SJ. Impairment of microtubule-dependent trafficking by overexpression of alpha-synuclein. The European Journal of Neuroscience. 2006;**24**(11):3153-3162. DOI: 10.1111/j.1460-9568.2006.05210.x

[35] Nakayama K, Suzuki Y, Yazawa I. Microtubule depolymerization suppresses alpha-synuclein accumulation in a mouse model of multiple system atrophy. The American Journal of Pathology. 2009;**174**(4):1471-1480. DOI: 10.2353/ajpath.2009.080503

[36] Nakayama K, Suzuki Y, Yazawa I. Binding of neuronal alpha-synuclein to beta-III tubulin and accumulation in a model of multiple system atrophy. Biochemical and Biophysical Research Communications. 2012;**417**(4):1170-1175. DOI: 10.1016/j.bbrc.2011.12.092

[37] Zhou RM, Huang YX, Li XL, Chen C, Shi Q, Wang GR, et al. Molecular interaction of alpha-synuclein with tubulin influences on the polymerization of microtubule in vitro and structure of microtubule in cells. Molecular Biology Reports. 2010;**37**(7):3183-3192. DOI: 10.1007/s11033-009-9899-2

[38] Eckert A, Nisbet R, Grimm A, Gotz J. March separate, strike together-role of phosphorylated TAU in mitochondrial dysfunction in Alzheimer's disease. Biochimica et Biophysica Acta. 2014;**1842**(8):1258-1266. DOI: 10.1016/j.bbadis.2013.08.013

[39] Prots I, Veber V, Brey S, Campioni S, Buder K, Riek R, et al. Alpha-synuclein oligomers impair neuronal microtubule-kinesin interplay. The Journal of Biological Chemistry. 2013;**288**(30):21742-21754. DOI: 10.1074/jbc.M113.451815

[40] Schapira AH. Mitochondria in the aetiology and pathogenesis of Parkinson's disease. Lancet Neurology. 2008;**7**(1):97-109. DOI: 10.1016/S1474-4422(07)70327-7

[41] Winslow AR, Chen CW, Corrochano S, Acevedo-Arozena A, Gordon DE, Peden AA, et al. Alpha-synuclein impairs macroautophagy: Implications for Parkinson's disease. The Journal of Cell Biology. 2010;**190**(6): 1023-1037. DOI: 10.1083/jcb.201003122

[42] Lynch-Day MA, Mao K, Wang K, Zhao M, Klionsky DJ. The role of autophagy in Parkinson's disease. Cold Spring Harbor Perspectives in Medicine. 2012;**2**(4):a009357. DOI: 10.1101/cshperspect.a009357

[43] Casley CS, Canevari L, Land JM, Clark JB, Sharpe MA. Beta-amyloid

inhibits integrated mitochondrial respiration and key enzyme activities. Journal of Neurochemistry. 2002;**80**(1):91-100

[44] Yang DS, Stavrides P, Mohan PS, Kaushik S, Kumar A, Ohno M, et al. Reversal of autophagy dysfunction in the TgCRND8 mouse model of Alzheimer's disease ameliorates amyloid pathologies and memory deficits. Brain. 2011;**134**(Pt 1):258-277. DOI: 10.1093/brain/awq341

[45] Dagda RK, Zhu J, Kulich SM, Chu CT. Mitochondrially localized ERK2 regulates mitophagy and autophagic cell stress: Implications for Parkinson's disease. Autophagy. 2008;**4**(6):770-782

[46] Kubli DA, Gustafsson AB. Mitochondria and mitophagy: The yin and yang of cell death control. Circulation Research. 2012;**111**(9):1208-1221. DOI: 10.1161/CIRCRESAHA.112.265819

[47] Yan J, Feng Z, Liu J, Shen W, Wang Y, Wertz K, et al. Enhanced autophagy plays a cardinal role in mitochondrial dysfunction in type 2 diabetic Goto-Kakizaki (GK) rats: Ameliorating effects of (−)-epigallocatechin-3-gallate. The Journal of Nutritional Biochemistry. 2012;**23**(7):716-724. DOI: 10.1016/j.jnutbio.2011.03.014

[48] Zhu JH, Horbinski C, Guo F, Watkins S, Uchiyama Y, Chu CT. Regulation of autophagy by extracellular signal-regulated protein kinases during 1-methyl-4-phenylpyridinium-induced cell death. The American Journal of Pathology. 2007;**170**(1):75-86. DOI: 10.2353/ajpath.2007.060524

[49] Rhein V, Song X, Wiesner A, Ittner LM, Baysang G, Meier F, et al. Amyloid-beta and tau synergistically impair the oxidative phosphorylation system in triple transgenic Alzheimer's disease mice. Proceedings of the National Academy of Sciences of the United States of America. 2009;**106**(47): 20057-20062. DOI: 10.1073/pnas.0905529106

[50] Liberski PP, Sikorska B, Bratosiewicz-Wasik J, Gajdusek DC, Brown P. Neuronal cell death in transmissible spongiform encephalopathies (prion diseases) revisited: From apoptosis to autophagy. The International Journal of Biochemistry & Cell Biology. 2004;**36**(12):2473-2490. DOI: 10.1016/j.biocel.2004.04.016

[51] Liberski PP, Brown DR, Sikorska B, Caughey B, Brown P. Cell death and autophagy in prion diseases (transmissible spongiform encephalopathies). Folia Neuropathologica. 2008;**46**(1):1-25

[52] Liberski PP, Gajdusek DC, Brown P. How do neurons degenerate in prion diseases or transmissible spongiform encephalopathies (TSEs): Neuronal autophagy revisited. Acta Neurobiologiae Experimentalis. 2002;**62**(3):141-147

[53] Shi Y. Caspase activation: Revisiting the induced proximity model. Cell. 2004;**117**(7):855-858. DOI: 10.1016/j.cell.2004.06.007

[54] Shi Y. Mechanisms of caspase activation and inhibition during apoptosis. Molecular Cell. 2002;**9**(3):459-470

[55] Sun X, Wu Y, Chen B, Zhang Z, Zhou W, Tong Y, et al. Regulator of calcineurin 1 (RCAN1) facilitates neuronal apoptosis through caspase-3 activation. The Journal of Biological Chemistry. 2011;**286**(11):9049-9062. DOI: 10.1074/jbc.M110.177519

[56] Eckert A, Marques CA, Keil U, Schussel K, Muller WE. Increased apoptotic cell death in sporadic and genetic Alzheimer's disease. Annals of the New York Academy of Sciences. 2003;**1010**:604-609

[57] Santos LE, Ferreira ST. Crosstalk between endoplasmic reticulum stress

and brain inflammation in Alzheimer's disease. Neuropharmacology. 2018;**136**(Pt B):350-360. DOI: 10.1016/j.neuropharm.2017.11.016

[58] Levine B, Mizushima N, Virgin HW. Autophagy in immunity and inflammation. Nature. 2011;**469**(7330):323-335. DOI: 10.1038/nature09782

[59] Salminen A, Kaarniranta K, Kauppinen A. Inflammaging: Disturbed interplay between autophagy and inflammasomes. Aging. 2012;**4**(3):166-175. DOI: 10.18632/aging.100444

[60] Saitoh T, Fujita N, Jang MH, Uematsu S, Yang BG, Satoh T, et al. Loss of the autophagy protein Atg16L1 enhances endotoxin-induced IL-1beta production. Nature. 2008;**456**(7219):264-268. DOI: 10.1038/nature07383

[61] Nakahira K, Haspel JA, Rathinam VA, Lee SJ, Dolinay T, Lam HC, et al. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. Nature Immunology. 2011;**12**(3):222-230. DOI: 10.1038/ni.1980

[62] Ghavami S, Shojaei S, Yeganeh B, Ande SR, Jangamreddy JR, Mehrpour M, et al. Autophagy and apoptosis dysfunction in neurodegenerative disorders. Progress in Neurobiology. 2014;**112**:24-49. DOI: 10.1016/j.pneurobio.2013.10.004

[63] Al-Hilaly YK, Williams TL, Stewart-Parker M, Ford L, Skaria E, Cole M, et al. A central role for dityrosine crosslinking of amyloid-beta in Alzheimer's disease. Acta Neuropathologica Communications. 2013;**1**:83. DOI: 10.1186/2051-5960-1-83

[64] Belay ED. Transmissible spongiform encephalopathies in humans. Annual Review of Microbiology. 1999;**53**:283-314. DOI: 10.1146/annurev.micro.53.1.283

[65] Los M, Mozoluk M, Ferrari D, Stepczynska A, Stroh C, Renz A, et al. Activation and caspase-mediated inhibition of PARP: A molecular switch between fibroblast necrosis and apoptosis in death receptor signaling. Molecular Biology of the Cell. 2002;**13**(3):978-988. DOI: 10.1091/mbc.01-05-0272

[66] Eguchi Y, Shimizu S, Tsujimoto Y. Intracellular ATP levels determine cell death fate by apoptosis or necrosis. Cancer Research. 1997;**57**(10):1835-1840

[67] Skulachev VP. Bioenergetic aspects of apoptosis, necrosis and mitoptosis. Apoptosis. 2006;**11**(4):473-485. DOI: 10.1007/s10495-006-5881-9

[68] Milisav I, Suput D, Ribaric S. Unfolded protein response and macroautophagy in Alzheimer's, Parkinson's and prion diseases. Molecules. 2015;**20**(12):22718-22756. DOI: 10.3390/molecules201219865

[69] Jucker M, Walker LC. Self-propagation of pathogenic protein aggregates in neurodegenerative diseases. Nature. 2013;**501**(7465):45-51. DOI: 10.1038/nature12481

[70] Guo JL, Lee VM. Cell-to-cell transmission of pathogenic proteins in neurodegenerative diseases. Nature Medicine. 2014;**20**(2):130-138. DOI: 10.1038/nm.3457

[71] Leist M, Jaattela M. Four deaths and a funeral: From caspases to alternative mechanisms. Nature Reviews Molecular Cell Biology. 2001;**2**(8):589-598. DOI: 10.1038/35085008

[72] Sims JL, Berger SJ, Berger NA. Poly(ADP-ribose) polymerase inhibitors preserve nicotinamide adenine dinucleotide and adenosine 5''-triphosphate pools in DNA-damaged cells: Mechanism of stimulation of unscheduled DNA synthesis. Biochemistry. 1983;**22**(22):5188-5194

[73] Szabo C, Dawson VL. Role of poly(ADP-ribose) synthetase in inflammation and ischaemia-reperfusion. Trends in Pharmacological Sciences. 1998;**19**(7):287-298

[74] Mizushima N. Autophagy: Process and function. Genes & Development. 2007;**21**(22):2861-2873. DOI: 10.1101/gad.1599207

[75] Keil E, Hocker R, Schuster M, Essmann F, Ueffing N, Hoffman B, et al. Phosphorylation of Atg5 by the Gadd45beta-MEKK4-p38 pathway inhibits autophagy. Cell Death and Differentiation. 2013;**20**(2):321-332. DOI: 10.1038/cdd.2012.129

[76] Taneike M, Yamaguchi O, Nakai A, Hikoso S, Takeda T, Mizote I, et al. Inhibition of autophagy in the heart induces age-related cardiomyopathy. Autophagy. 2010;**6**(5):600-606. DOI: 10.4161/auto.6.5.11947

[77] Lepine S, Allegood JC, Edmonds Y, Milstien S, Spiegel S. Autophagy induced by deficiency of sphingosine-1-phosphate phosphohydrolase 1 is switched to apoptosis by calpain-mediated autophagy-related gene 5 (Atg5) cleavage. The Journal of Biological Chemistry. 2011;**286**(52):44380-44390. DOI: 10.1074/jbc.M111.257519

[78] Elfawy HA, Das B. Crosstalk between mitochondrial dysfunction, oxidative stress, and age related neurodegenerative disease: Etiologies and therapeutic strategies. Life Sciences. 2019;**218**:165-184. DOI: 10.1016/j.lfs.2018.12.029

[79] Hamilton A, Zamponi GW, Ferguson SS. Glutamate receptors function as scaffolds for the regulation of beta-amyloid and cellular prion protein signaling complexes. Molecular Brain. 2015;**8**:18. DOI: 10.1186/s13041-015-0107-0

[80] Stys PK, You H, Zamponi GW. Copper-dependent regulation of NMDA receptors by cellular prion protein: Implications for neurodegenerative disorders. The Journal of Physiology. 2012;**590**(6):1357-1368. DOI: 10.1113/jphysiol.2011.225276

[81] Khosravani H, Zhang Y, Tsutsui S, Hameed S, Altier C, Hamid J, et al. Prion protein attenuates excitotoxicity by inhibiting NMDA receptors. The Journal of Cell Biology. 2008;**181**(3):551-565. DOI: 10.1083/jcb.200711002

[82] Shi M, Zhang T, Sun L, Luo Y, Liu DH, Xie ST, et al. Calpain, Atg5 and Bak play important roles in the crosstalk between apoptosis and autophagy induced by influx of extracellular calcium. Apoptosis. 2013;**18**(4):435-451. DOI: 10.1007/s10495-012-0786-2

[83] Xia HG, Zhang L, Chen G, Zhang T, Liu J, Jin M, et al. Control of basal autophagy by calpain1 mediated cleavage of ATG5. Autophagy. 2010;**6**(1):61-66

[84] Zhu X, Messer JS, Wang Y, Lin F, Cham CM, Chang J, et al. Cytosolic HMGB1 controls the cellular autophagy/apoptosis checkpoint during inflammation. The Journal of Clinical Investigation. 2015;**125**(3):1098-1110. DOI: 10.1172/JCI76344

[85] Wei Y, Zou Z, Becker N, Anderson M, Sumpter R, Xiao G, et al. EGFR-mediated Beclin 1 phosphorylation in autophagy suppression, tumor progression, and tumor chemoresistance. Cell. 2013;**154**(6):1269-1284. DOI: 10.1016/j.cell.2013.08.015

[86] Van Humbeeck C, Cornelissen T, Vandenberghe W. Ambra1: A parkin-binding protein involved in mitophagy. Autophagy. 2011;**7**(12):1555-1556

[87] Luo S, Rubinsztein DC. BCL2L11/BIM: A novel molecular link between autophagy and apoptosis. Autophagy. 2013;**9**(1):104-105. DOI: 10.4161/auto.22399

[88] He MX, He YW. CFLAR/c-FLIPL: A star in the autophagy, apoptosis and necroptosis alliance. Autophagy. 2013;**9**(5):791-793. DOI: 10.4161/auto.23785

[89] Hou W, Han J, Lu C, Goldstein LA, Rabinowich H. Autophagic degradation of active caspase-8: A crosstalk mechanism between autophagy and apoptosis. Autophagy. 2010;**6**(7): 891-900. DOI: 10.4161/auto.6.7.13038

[90] Cho DH, Jo YK, Hwang JJ, Lee YM, Roh SA, Kim JC. Caspase-mediated cleavage of ATG6/Beclin-1 links apoptosis to autophagy in HeLa cells. Cancer Letters. 2009;**274**(1):95-100. DOI: 10.1016/j.canlet.2008.09.004

[91] Wirawan E, Vande Walle L, Kersse K, Cornelis S, Claerhout S, Vanoverberghe I, et al. Caspase-mediated cleavage of Beclin-1 inactivates Beclin-1-induced autophagy and enhances apoptosis by promoting the release of proapoptotic factors from mitochondria. Cell Death & Disease. 2010;**1**:e18. DOI: 10.1038/cddis.2009.16

[92] Luo S, Rubinsztein DC. Apoptosis blocks Beclin 1-dependent autophagosome synthesis: An effect rescued by Bcl-xL. Cell Death and Differentiation. 2010;**17**(2):268-277. DOI: 10.1038/cdd.2009.121

[93] Kang R, Zeh HJ, Lotze MT, Tang D. The Beclin 1 network regulates autophagy and apoptosis. Cell Death and Differentiation. 2011;**18**(4):571-580. DOI: 10.1038/cdd.2010.191

[94] Zhou F, Yang Y, Xing D. Bcl-2 and Bcl-xL play important roles in the crosstalk between autophagy and apoptosis. The FEBS Journal. 2011;**278**(3):403-413. DOI: 10.1111/j.1742-4658.2010.07965.x

[95] Youle RJ, Strasser A. The BCL-2 protein family: Opposing activities that mediate cell death. Nature Reviews Molecular Cell Biology. 2008;**9**(1):47-59. DOI: 10.1038/nrm2308

[96] Wei MC, Zong WX, Cheng EH, Lindsten T, Panoutsakopoulou V, Ross AJ, et al. Proapoptotic BAX and BAK: A requisite gateway to mitochondrial dysfunction and death. Science. 2001;**292**(5517):727-730. DOI: 10.1126/science.1059108

[97] Zong WX, Lindsten T, Ross AJ, MacGregor GR, Thompson CB. BH3-only proteins that bind pro-survival Bcl-2 family members fail to induce apoptosis in the absence of Bax and Bak. Genes & Development. 2001;**15**(12):1481-1486. DOI: 10.1101/gad.897601

[98] Kang MH, Reynolds CP. Bcl-2 inhibitors: Targeting mitochondrial apoptotic pathways in cancer therapy. Clinical Cancer Research. 2009;**15**(4):1126-1132. DOI: 10.1158/1078-0432.CCR-08-0144

[99] Danial NN. BCL-2 family proteins: Critical checkpoints of apoptotic cell death. Clinical Cancer Research. 2007;**13**(24):7254-7263. DOI: 10.1158/1078-0432.Ccr-07-1598

[100] Cheng EH, Wei MC, Weiler S, Flavell RA, Mak TW, Lindsten T, et al. BCL-2, BCL-X(L) sequester BH3 domain-only molecules preventing BAX- and BAK-mediated mitochondrial apoptosis. Molecular Cell. 2001;**8**(3):705-711

[101] Willis SN, Chen L, Dewson G, Wei A, Naik E, Fletcher JI, et al. Proapoptotic Bak is sequestered by Mcl-1 and Bcl-xL, but not Bcl-2, until displaced by BH3-only proteins. Genes & Development. 2005;**19**(11):1294-1305. DOI: 10.1101/gad.1304105

[102] Werner AB, de Vries E, Tait SW, Bontjer I, Borst J. Bcl-2 family member Bfl-1/A1 sequesters truncated bid to inhibit is collaboration with pro-apoptotic Bak or Bax. The

Journal of Biological Chemistry. 2002;**277**(25):22781-22788. DOI: 10.1074/jbc.M201469200

[103] Kuwana T, Bouchier-Hayes L, Chipuk JE, Bonzon C, Sullivan BA, Green DR, et al. BH3 domains of BH3-only proteins differentially regulate Bax-mediated mitochondrial membrane permeabilization both directly and indirectly. Molecular Cell. 2005;**17**(4): 525-535. DOI: 10.1016/j.molcel.2005.02.003

[104] Kim H, Rafiuddin-Shah M, Tu HC, Jeffers JR, Zambetti GP, Hsieh JJ, et al. Hierarchical regulation of mitochondrion-dependent apoptosis by BCL-2 subfamilies. Nature Cell Biology. 2006;**8**(12):1348-1358. DOI: 10.1038/ncb1499

[105] Erlich S, Mizrachy L, Segev O, Lindenboim L, Zmira O, Adi-Harel S, et al. Differential interactions between Beclin 1 and Bcl-2 family members. Autophagy. 2007;**3**(6):561-568

[106] Maiuri MC, Criollo A, Tasdemir E, Vicencio JM, Tajeddine N, Hickman JA, et al. BH3-only proteins and BH3 mimetics induce autophagy by competitively disrupting the interaction between Beclin 1 and Bcl-2/Bcl-X(L). Autophagy. 2007;**3**(4):374-376

[107] Zalckvar E, Berissi H, Eisenstein M, Kimchi A. Phosphorylation of Beclin 1 by DAP-kinase promotes autophagy by weakening its interactions with Bcl-2 and Bcl-XL. Autophagy. 2009;**5**(5):720-722

[108] Wei Y, Sinha S, Levine B. Dual role of JNK1-mediated phosphorylation of Bcl-2 in autophagy and apoptosis regulation. Autophagy. 2008;**4**(7):949-951

[109] Kitamura Y, Shimohama S, Kamoshima W, Ota T, Matsuoka Y, Nomura Y, et al. Alteration of proteins regulating apoptosis, Bcl-2, Bcl-x, Bax, Bak, Bad, ICH-1 and CPP32, in Alzheimer's disease. Brain Research. 1998;**780**(2):260-269

[110] Roucou X, Gains M, LeBlanc AC. Neuroprotective functions of prion protein. Journal of Neuroscience Research. 2004;**75**(2):153-161. DOI: 10.1002/jnr.10864

[111] Roucou X, Giannopoulos PN, Zhang Y, Jodoin J, Goodyer CG, LeBlanc A. Cellular prion protein inhibits proapoptotic Bax conformational change in human neurons and in breast carcinoma MCF-7 cells. Cell Death and Differentiation. 2005;**12**(7):783-795. DOI: 10.1038/sj.cdd.4401629

[112] Roucou X, Guo Q, Zhang Y, Goodyer CG, LeBlanc AC. Cytosolic prion protein is not toxic and protects against Bax-mediated cell death in human primary neurons. The Journal of Biological Chemistry. 2003;**278**(42):40877-40881. DOI: 10.1074/jbc.M306177200

[113] Rehker J, Rodhe J, Nesbitt RR, Boyle EA, Martin BK, Lord J, et al. Caspase-8, association with Alzheimer's disease and functional analysis of rare variants. PLoS One. 2017;**12**(10):e0185777. DOI: 10.1371/journal.pone.0185777

[114] Feng S, Yang Y, Mei Y, Ma L, Zhu DE, Hoti N, et al. Cleavage of RIP3 inactivates its caspase-independent apoptosis pathway by removal of kinase domain. Cellular Signalling. 2007;**19**(10):2056-2067. DOI: 10.1016/j.cellsig.2007.05.016

[115] O'Donnell MA, Perez-Jimenez E, Oberst A, Ng A, Massoumi R, Xavier R, et al. Caspase 8 inhibits programmed necrosis by processing CYLD. Nature Cell Biology. 2011;**13**(12):1437-1442. DOI: 10.1038/ncb2362

[116] Rebe C, Cathelin S, Launay S, Filomenko R, Prevotat L, L'Ollivier C, et al. Caspase-8 prevents sustained

activation of NF-kappaB in monocytes undergoing macrophagic differentiation. Blood. 2007;**109**(4):1442-1450. DOI: 10.1182/blood-2006-03-011585

[117] Moquin DM, McQuade T, Chan FK. CYLD deubiquitinates RIP1 in the TNFalpha-induced necrosome to facilitate kinase activation and programmed necrosis. PLoS One. 2013;**8**(10):e76841. DOI: 10.1371/journal.pone.0076841

[118] Salvesen GS, Walsh CM. Functions of caspase 8: The identified and the mysterious. Seminars in Immunology. 2014;**26**(3):246-252. DOI: 10.1016/j.smim.2014.03.005

[119] Bjorkblom B, Vainio JC, Hongisto V, Herdegen T, Courtney MJ, Coffey ET. All JNKs can kill, but nuclear localization is critical for neuronal death. The Journal of Biological Chemistry. 2008;**283**(28):19704-19713. DOI: 10.1074/jbc.M707744200

[120] Dhanasekaran DN, Reddy EP. JNK-signaling: A multiplexing hub in programmed cell death. Genes & Cancer. 2017;**8**(9-10):682-694. DOI: 10.18632/genesandcancer.155

[121] Davis RJ. Signal transduction by the JNK group of MAP kinases. Cell. 2000;**103**(2):239-252

[122] Chang L, Karin M. Mammalian MAP kinase signalling cascades. Nature. 2001;**410**(6824):37-40. DOI: 10.1038/35065000

[123] Dhanasekaran DN, Reddy EP. JNK signaling in apoptosis. Oncogene. 2008;**27**(48):6245-6251. DOI: 10.1038/onc.2008.301

[124] Turjanski AG, Vaque JP, Gutkind JS. MAP kinases and the control of nuclear events. Oncogene. 2007;**26**(22):3240-3253. DOI: 10.1038/sj.onc.1210415

[125] Fan M, Chambers TC. Role of mitogen-activated protein kinases in the response of tumor cells to chemotherapy. Drug Resistance Updates. 2001;**4**(4):253-267. DOI: 10.1054/drup.2001.0214

[126] Johnson GL, Nakamura K. The c-Jun kinase/stress-activated pathway: Regulation, function and role in human disease. Biochimica et Biophysica Acta. 2007;**1773**(8):1341-1348. DOI: 10.1016/j.bbamcr.2006.12.009

[127] Fuchs SY, Adler V, Buschmann T, Yin Z, Wu X, Jones SN, et al. JNK targets p53 ubiquitination and degradation in nonstressed cells. Genes & Development. 1998;**12**(17):2658-2663

[128] Oleinik NV, Krupenko NI, Krupenko SA. Cooperation between JNK1 and JNK2 in activation of p53 apoptotic pathway. Oncogene. 2007;**26**(51):7222-7230. DOI: 10.1038/sj.onc.1210526

[129] Tournier C, Hess P, Yang DD, Xu J, Turner TK, Nimnual A, et al. Requirement of JNK for stress-induced activation of the cytochrome c-mediated death pathway. Science. 2000;**288**(5467):870-874

[130] Lei K, Nimnual A, Zong WX, Kennedy NJ, Flavell RA, Thompson CB, et al. The Bax subfamily of Bcl2-related proteins is essential for apoptotic signal transduction by c-Jun NH(2)-terminal kinase. Molecular and Cellular Biology. 2002;**22**(13):4929-4942

[131] Mandal M, Olson DJ, Sharma T, Vadlamudi RK, Kumar R. Butyric acid induces apoptosis by up-regulating Bax expression via stimulation of the c-Jun N-terminal kinase/activation protein-1 pathway in human colon cancer cells. Gastroenterology. 2001;**120**(1):71-78

[132] Papadakis ES, Finegan KG, Wang X, Robinson AC, Guo C, Kayahara M, et al. The regulation of Bax by c-Jun N-terminal protein kinase (JNK) is a prerequisite

to the mitochondrial-induced apoptotic pathway. FEBS Letters. 2006;**580**(5):1320-1326. DOI: 10.1016/j.febslet.2006.01.053

[133] Tsuruta F, Sunayama J, Mori Y, Hattori S, Shimizu S, Tsujimoto Y, et al. JNK promotes Bax translocation to mitochondria through phosphorylation of 14-3-3 proteins. The EMBO Journal. 2004;**23**(8):1889-1899. DOI: 10.1038/sj.emboj.7600194

[134] Donovan N, Becker EB, Konishi Y, Bonni A. JNK phosphorylation and activation of BAD couples the stress-activated signaling pathway to the cell death machinery. The Journal of Biological Chemistry. 2002;**277**(43):40944-40949. DOI: 10.1074/jbc.M206113200

[135] Wang XT, Pei DS, Xu J, Guan QH, Sun YF, Liu XM, et al. Opposing effects of Bad phosphorylation at two distinct sites by Akt1 and JNK1/2 on ischemic brain injury. Cellular Signalling. 2007;**19**(9):1844-1856. DOI: 10.1016/j.cellsig.2007.04.005

[136] Adams JM, Cory S. Bcl-2-regulated apoptosis: Mechanism and therapeutic potential. Current Opinion in Immunology. 2007;**19**(5):488-496. DOI: 10.1016/j.coi.2007.05.004

[137] Lei K, Davis RJ. JNK phosphorylation of Bim-related members of the Bcl2 family induces Bax-dependent apoptosis. Proceedings of the National Academy of Sciences of the United States of America. 2003;**100**(5):2432-2437. DOI: 10.1073/pnas.0438011100

[138] Putcha GV, Le S, Frank S, Besirli CG, Clark K, Chu B, et al. JNK-mediated BIM phosphorylation potentiates BAX-dependent apoptosis. Neuron. 2003;**38**(6):899-914

[139] Marani M, Tenev T, Hancock D, Downward J, Lemoine NR. Identification of novel isoforms of the BH3 domain protein Bim which directly activate Bax to trigger apoptosis. Molecular and Cellular Biology. 2002;**22**(11):3577-3589

[140] Letai A, Bassik MC, Walensky LD, Sorcinelli MD, Weiler S, Korsmeyer SJ. Distinct BH3 domains either sensitize or activate mitochondrial apoptosis, serving as prototype cancer therapeutics. Cancer Cell. 2002;**2**(3):183-192

[141] Willis SN, Fletcher JI, Kaufmann T, van Delft MF, Chen L, Czabotar PE, et al. Apoptosis initiated when BH3 ligands engage multiple Bcl-2 homologs, not Bax or Bak. Science. 2007;**315**(5813):856-859. DOI: 10.1126/science.1133289

[142] Hubner A, Barrett T, Flavell RA, Davis RJ. Multisite phosphorylation regulates Bim stability and apoptotic activity. Molecular Cell. 2008;**30**(4):415-425. DOI: 10.1016/j.molcel.2008.03.025

[143] Yamamoto K, Ichijo H, Korsmeyer SJ. BCL-2 is phosphorylated and inactivated by an ASK1/Jun N-terminal protein kinase pathway normally activated at G(2)/M. Molecular and Cellular Biology. 1999;**19**(12):8469-8478

[144] Walczak H. Death receptor-ligand systems in cancer, cell death, and inflammation. Cold Spring Harbor Perspectives in Biology. 2013;**5**(5):a008698. DOI: 10.1101/cshperspect.a008698

[145] Papa S, Zazzeroni F, Pham CG, Bubici C, Franzoso G. Linking JNK signaling to NF-kappaB: A key to survival. Journal of Cell Science. 2004;**117**(Pt 22):5197-5208. DOI: 10.1242/jcs.01483

[146] Higuchi H, Grambihler A, Canbay A, Bronk SF, Gores GJ. Bile acids up-regulate death receptor 5/TRAIL-receptor 2 expression via a c-Jun

N-terminal kinase-dependent pathway involving Sp1. The Journal of Biological Chemistry. 2004;**279**(1):51-60. DOI: 10.1074/jbc.M309476200

[147] Zou W, Liu X, Yue P, Zhou Z, Sporn MB, Lotan R, et al. c-Jun NH2-terminal kinase-mediated up-regulation of death receptor 5 contributes to induction of apoptosis by the novel synthetic triterpenoid methyl-2-cyano-3,12-dioxooleana-1, 9-dien-28-oate in human lung cancer cells. Cancer Research. 2004;**64**(20):7570-7578. DOI: 10.1158/0008-5472.CAN-04-1238

[148] Jin HO, Park IC, An S, Lee HC, Woo SH, Hong YJ, et al. Up-regulation of Bak and Bim via JNK downstream pathway in the response to nitric oxide in human glioblastoma cells. Journal of Cellular Physiology. 2006;**206**(2): 477-486. DOI: 10.1002/jcp.20488

[149] Chen YJ, Liu WH, Kao PH, Wang JJ, Chang LS. Involvement of p38 MAPK- and JNK-modulated expression of Bcl-2 and Bax in Naja nigricollis CMS-9-induced apoptosis of human leukemia K562 cells. Toxicon. 2010;**55**(7):1306-1316. DOI: 10.1016/j.toxicon.2010.01.024

[150] Deng Y, Ren X, Yang L, Lin Y, Wu X. A JNK-dependent pathway is required for TNFalpha-induced apoptosis. Cell. 2003;**115**(1):61-70

[151] Silke J, Meier P. Inhibitor of apoptosis (IAP) proteins-modulators of cell death and inflammation. Cold Spring Harbor Perspectives in Biology. 2013;**5**(2):1-19. DOI: 10.1101/cshperspect.a008730

[152] Ploia C, Antoniou X, Sclip A, Grande V, Cardinetti D, et al. JNK plays a key role in tau hyperphosphorylation in Alzheimer's disease models. Journal of Alzheimer's Disease. 2011;**26**(2):315-329. DOI: 10.3233/JAD-2011-110320. PubMed PMID: 21628793

[153] Morishima Y, Gotoh Y, Zieg J, Barrett T, Takano H, Flavell R, et al. Beta-amyloid induces neuronal apoptosis via a mechanism that involves the c-Jun N-terminal kinase pathway and the induction of Fas ligand. The Journal of Neuroscience. 2001;**21**(19):7551-7560

[154] Minogue AM, Schmid AW, Fogarty MP, Moore AC, Campbell VA, Herron CE, et al. Activation of the c-Jun N-terminal kinase signaling cascade mediates the effect of amyloid-beta on long term potentiation and cell death in hippocampus: A role for interleukin-1beta? The Journal of Biological Chemistry. 2003;**278**(30):27971-27980. DOI: 10.1074/jbc.M302530200

[155] Zhu X, Raina AK, Rottkamp CA, Aliev G, Perry G, Boux H, et al. Activation and redistribution of c-Jun N-terminal kinase/stress activated protein kinase in degenerating neurons in Alzheimer's disease. Journal of Neurochemistry. 2001;**76**(2):435-441

[156] Ferrer I, Blanco R, Carmona M, Puig B. Phosphorylated mitogen-activated protein kinase (MAPK/ERK-P), protein kinase of 38 kDa (p38-P), stress-activated protein kinase (SAPK/JNK-P), and calcium/calmodulin-dependent kinase II (CaM kinase II) are differentially expressed in tau deposits in neurons and glial cells in tauopathies. Journal of Neural Transmission (Vienna). 2001;**108**(12):1397-1415. DOI: 10.1007/s007020100016

[157] Bellucci A, Rosi MC, Grossi C, Fiorentini A, Luccarini I, Casamenti F. Abnormal processing of tau in the brain of aged TgCRND8 mice. Neurobiology of Disease. 2007;**27**(3):328-338. DOI: 10.1016/j.nbd.2007.06.008

[158] Ma QL, Yang F, Rosario ER, Ubeda OJ, Beech W, Gant DJ, et al. Beta-amyloid oligomers induce phosphorylation of tau and inactivation of insulin receptor substrate via

c-Jun N-terminal kinase signaling: Suppression by omega-3 fatty acids and curcumin. The Journal of Neuroscience. 2009;**29**(28):9078-9089. DOI: 10.1523/JNEUROSCI.1071-09.2009

[159] Vogel J, Anand VS, Ludwig B, Nawoschik S, Dunlop J, Braithwaite SP. The JNK pathway amplifies and drives subcellular changes in tau phosphorylation. Neuropharmacology. 2009;**57**(5-6):539-550. DOI: 10.1016/j.neuropharm.2009.07.021

[160] Drewes G, Ebneth A, Mandelkow EM. MAPs, MARKs and microtubule dynamics. Trends in Biochemical Sciences. 1998;**23**(8):307-311

[161] Kosik KS, McConlogue L. Microtubule-associated protein function: Lessons from expression in Spodoptera frugiperda cells. Cell Motility and the Cytoskeleton. 1994;**28**(3):195-198. DOI: 10.1002/cm.970280302

[162] Illenberger S, Zheng-Fischhofer Q, Preuss U, Stamer K, Baumann K, Trinczek B, et al. The endogenous and cell cycle-dependent phosphorylation of tau protein in living cells: Implications for Alzheimer's disease. Molecular Biology of the Cell. 1998;**9**(6):1495-1512

[163] Mandelkow EM, Biernat J, Drewes G, Gustke N, Trinczek B, Mandelkow E. Tau domains, phosphorylation, and interactions with microtubules. Neurobiology of Aging. 1995;**16**(3):355-362. Discussion: 362-353

[164] Trojanowski JQ, Lee VM. Phosphorylation of paired helical filament tau in Alzheimer's disease neurofibrillary lesions: Focusing on phosphatases. The FASEB Journal. 1995;**9**(15):1570-1576

[165] Delacourte A, Buee L. Normal and pathological tau proteins as factors for microtubule assembly. International Review of Cytology. 1997;**171**:167-224

[166] Mandelkow EM, Mandelkow E. Tau in Alzheimer's disease. Trends in Cell Biology. 1998;**8**(11):425-427

[167] Linkermann A, Green DR. Necroptosis. The New England Journal of Medicine. 2014;**370**(5):455-465. DOI: 10.1056/NEJMra1310050

[168] Wang Z, Jiang H, Chen S, Du F, Wang X. The mitochondrial phosphatase PGAM5 functions at the convergence point of multiple necrotic death pathways. Cell. 2012;**148**(1-2):228-243. DOI: 10.1016/j.cell.2011.11.030

[169] Cai Z, Jitkaew S, Zhao J, Chiang HC, Choksi S, Liu J, et al. Plasma membrane translocation of trimerized MLKL protein is required for TNF-induced necroptosis. Nature Cell Biology. 2014;**16**(1):55-65. DOI: 10.1038/ncb2883

[170] Sun W, Wu X, Gao H, Yu J, Zhao W, Lu JJ, et al. Cytosolic calcium mediates RIP1/RIP3 complex-dependent necroptosis through JNK activation and mitochondrial ROS production in human colon cancer cells. Free Radical Biology & Medicine. 2017;**108**:433-444. DOI: 10.1016/j.freeradbiomed.2017.04.010

[171] Kamata H, Honda S, Maeda S, Chang L, Hirata H, Karin M. Reactive oxygen species promote TNFalpha-induced death and sustained JNK activation by inhibiting MAP kinase phosphatases. Cell. 2005;**120**(5):649-661. DOI: 10.1016/j.cell.2004.12.041

[172] Lee JS, Li Q, Lee JY, Lee SH, Jeong JH, Lee HR, et al. FLIP-mediated autophagy regulation in cell death control. Nature Cell Biology. 2009;**11**(11):1355-1362. DOI: 10.1038/ncb1980

[173] Fujita K, Motoki K, Tagawa K, Chen X, Hama H, Nakajima K, et al. HMGB1, a pathogenic molecule that induces neurite degeneration

via TLR4-MARCKS, is a potential therapeutic target for Alzheimer's disease. Scientific Reports. 2016;**6**:31895. DOI: 10.1038/srep31895

[174] Paudel YN, Shaikh MF, Chakraborti A, Kumari Y, Aledo-Serrano A, Aleksovska K, et al. HMGB1: A common biomarker and potential target for TBI, neuroinflammation, epilepsy, and cognitive dysfunction. Frontiers in Neuroscience. 2018;**12**:628. DOI: 10.3389/fnins.2018.00628

[175] Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. Lancet Neurology. 2015;**14**(4):388-405. DOI: 10.1016/S1474-4422(15)70016-5

[176] Tansey MG, Goldberg MS. Neuroinflammation in Parkinson's disease: Its role in neuronal death and implications for therapeutic intervention. Neurobiology of Disease. 2010;**37**(3):510-518. DOI: 10.1016/j.nbd.2009.11.004

[177] Frank MG, Weber MD, Fonken LK, Hershman SA, Watkins LR, Maier SF. The redox state of the alarmin HMGB1 is a pivotal factor in neuroinflammatory and microglial priming: A role for the NLRP3 inflammasome. Brain, Behavior, and Immunity. 2016;**55**:215-224. DOI: 10.1016/j.bbi.2015.10.009

[178] Takata K, Kitamura Y, Tsuchiya D, Kawasaki T, Taniguchi T, Shimohama S. High mobility group box protein-1 inhibits microglial Abeta clearance and enhances Abeta neurotoxicity. Journal of Neuroscience Research. 2004;**78**(6): 880-891. DOI: 10.1002/jnr.20340

[179] Takata K, Takada T, Ito A, Asai M, Tawa M, Saito Y, et al. Microglial amyloid-beta1-40 phagocytosis dysfunction is caused by high-mobility group box protein-1: Implications for the pathological progression of Alzheimer's disease. International Journal of Alzheimer's Disease. 2012;**2012**:685739. DOI: 10.1155/2012/685739

[180] Ma Y, Shi Q, Wang J, Xiao K, Sun J, Lv Y, et al. Reduction of NF-kappaB (p65) in scrapie-infected cultured cells and in the brains of scrapie-infected rodents. ACS Chemical Neuroscience. 2017;**8**(11):2535-2548. DOI: 10.1021/acschemneuro.7b00273

[181] Barger SW, Mattson MP. Induction of neuroprotective kappa B-dependent transcription by secreted forms of the Alzheimer's beta-amyloid precursor. Brain Research Molecular Brain Research. 1996;**40**(1):116-126

[182] Guo Q, Robinson N, Mattson MP. Secreted beta-amyloid precursor protein counteracts the proapoptotic action of mutant presenilin-1 by activation of NF-kappaB and stabilization of calcium homeostasis. The Journal of Biological Chemistry. 1998;**273**(20):12341-12351

[183] Mattson MP, Goodman Y, Luo H, Fu W, Furukawa K. Activation of NF-kappaB protects hippocampal neurons against oxidative stress-induced apoptosis: Evidence for induction of manganese superoxide dismutase and suppression of peroxynitrite production and protein tyrosine nitration. Journal of Neuroscience Research. 1997;**49**(6):681-697. DOI: 10.1002/(SICI)1097-4547(19970915)49:6<681:AID-JNR3>3.0.CO;2-3

[184] Barger SW, Horster D, Furukawa K, Goodman Y, Krieglstein J, Mattson MP. Tumor necrosis factors alpha and beta protect neurons against amyloid beta-peptide toxicity: Evidence for involvement of a kappa B-binding factor and attenuation of peroxide and Ca^{2+} accumulation. Proceedings of the National Academy of Sciences of the United States of America. 1995;**92**(20):9328-9332

[185] Hunot S, Brugg B, Ricard D, Michel PP, Muriel MP, Ruberg M, et al. Nuclear translocation of NF-kappaB is increased in dopaminergic neurons

of patients with parkinson disease. Proceedings of the National Academy of Sciences of the United States of America. 1997;**94**(14):7531-7536

[186] Kihara A, Kabeya Y, Ohsumi Y, Yoshimori T. Beclin-phosphatidylinositol 3-kinase complex functions at the trans-Golgi network. EMBO Reports. 2001;**2**(4):330-335. DOI: 10.1093/embo-reports/kve061

[187] Kang R, Livesey KM, Zeh HJ, Loze MT, Tang D. HMGB1: A novel Beclin 1-binding protein active in autophagy. Autophagy. 2010;**6**(8):1209-1211

[188] Morselli E, Galluzzi L, Kepp O, Marino G, Michaud M, Vitale I, et al. Oncosuppressive functions of autophagy. Antioxidants & Redox Signaling. 2011;**14**(11):2251-2269. DOI: 10.1089/ars.2010.3478

[189] Shih RH, Wang CY, Yang CM. NF-kappaB signaling pathways in neurological inflammation: A mini review. Frontiers in Molecular Neuroscience. 2015;**8**:77. DOI: 10.3389/fnmol.2015.00077

[190] Milne JC, Denu JM. The Sirtuin family: Therapeutic targets to treat diseases of aging. Current Opinion in Chemical Biology. 2008;**12**(1):11-17. DOI: 10.1016/j.cbpa.2008.01.019

[191] Lee IH, Cao L, Mostoslavsky R, Lombard DB, Liu J, Bruns NE, et al. A role for the NAD-dependent deacetylase Sirt1 in the regulation of autophagy. Proceedings of the National Academy of Sciences of the United States of America. 2008;**105**(9):3374-3379. DOI: 10.1073/pnas.0712145105

[192] Narayan N, Lee IH, Borenstein R, Sun J, Wong R, Tong G, et al. The NAD-dependent deacetylase SIRT2 is required for programmed necrosis. Nature. 2012;**492**(7428):199-204. DOI: 10.1038/nature11700

[193] Kim D, Nguyen MD, Dobbin MM, Fischer A, Sananbenesi F, Rodgers JT, et al. SIRT1 deacetylase protects against neurodegeneration in models for Alzheimer's disease and amyotrophic lateral sclerosis. The EMBO Journal. 2007;**26**(13):3169-3179. DOI: 10.1038/sj.emboj.7601758

[194] Julien C, Tremblay C, Emond V, Lebbadi M, Salem N Jr, Bennett DA, et al. Sirtuin 1 reduction parallels the accumulation of tau in Alzheimer disease. Journal of Neuropathology and Experimental Neurology. 2009;**68**(1):48-58. DOI: 10.1097/NEN.0b013e3181922348

[195] Chipuk JE, Kuwana T, Bouchier-Hayes L, Droin NM, Newmeyer DD, Schuler M, et al. Direct activation of Bax by p53 mediates mitochondrial membrane permeabilization and apoptosis. Science. 2004;**303**(5660):1010-1014. DOI: 10.1126/science.1092734

[196] Nakano K, Vousden KH. PUMA, a novel proapoptotic gene, is induced by p53. Molecular Cell. 2001;**7**(3):683-694

[197] Chipuk JE, Bouchier-Hayes L, Kuwana T, Newmeyer DD, Green DR. PUMA couples the nuclear and cytoplasmic proapoptotic function of p53. Science. 2005;**309**(5741):1732-1735. DOI: 10.1126/science.1114297

[198] Mah LY, O'Prey J, Baudot AD, Hoekstra A, Ryan KM. DRAM-1 encodes multiple isoforms that regulate autophagy. Autophagy. 2012;**8**(1):18-28. DOI: 10.4161/auto.8.1.18077

[199] Gao W, Shen Z, Shang L, Wang X. Upregulation of human autophagy-initiation kinase ULK1 by tumor suppressor p53 contributes to DNA-damage-induced cell death. Cell Death and Differentiation. 2011;**18**(10):1598-1607. DOI: 10.1038/cdd.2011.33

[200] Feng Z, Zhang H, Levine AJ, Jin S. The coordinate regulation of the p53 and mTOR pathways in cells. Proceedings of the National Academy of Sciences of the United States of America. 2005;**102**(23):8204-8209. DOI: 10.1073/pnas.0502857102

[201] Crighton D, Wilkinson S, O'Prey J, Syed N, Smith P, Harrison PR, et al. DRAM, a p53-induced modulator of autophagy, is critical for apoptosis. Cell. 2006;**126**(1):121-134. DOI: 10.1016/j.cell.2006.05.034

[202] Merlo P, Frost B, Peng S, Yang YJ, Park PJ, Feany M. p53 prevents neurodegeneration by regulating synaptic genes. Proceedings of the National Academy of Sciences of the United States of America. 2014;**111**(50):18055-18060. DOI: 10.1073/pnas.1419083111

[203] Kitamura Y, Shimohama S, Kamoshima W, Matsuoka Y, Nomura Y, et al. Changes of p53 in the brains of patients with Alzheimer's disease. Biochemical and Biophysical Research Communications. 1997;**232**:418-421

[204] Su JH, Deng G, Cotman CW. Bax protein expression is increased in Alzheimer's brain: Correlations with DNA damage, Bcl-2 expression, and brain pathology. Journal of Neuropathology and Experimental Neurology. 1997;**56**(1):86-93

[205] Farmer KM, Carretero-Murillo M, McAllen S, Sarkar P, Kayed R. Tau and P53 in Alzheimer's disease. Alzheimer's & Dementia. 2017;**13**(7):1505. DOI: 10.1016/j.jalz.2017.07.617

[206] Goodall ML, Fitzwalter BE, Zahedi S, Wu M, Rodriguez D, Mulcahy-Levy JM, et al. The autophagy machinery controls cell death switching between apoptosis and necroptosis. Developmental Cell. 2016;**37**(4):337-349. DOI: 10.1016/j.devcel.2016.04.018

[207] Moscat J, Diaz-Meco MT. p62 at the crossroads of autophagy, apoptosis, and cancer. Cell. 2009;**137**(6):1001-1004. DOI: 10.1016/j.cell.2009.05.023

[208] Salminen A, Kaarniranta K, Haapasalo A, Hiltunen M, Soininen H, Alafuzoff I. Emerging role of p62/sequestosome-1 in the pathogenesis of Alzheimer's disease. Progress in Neurobiology. 2012;**96**(1):87-95. DOI: 10.1016/j.pneurobio.2011.11.005

[209] Komatsu M, Kageyama S, Ichimura Y. p62/SQSTM1/A170: Physiology and pathology. Pharmacological Research. 2012;**66**(6):457-462. DOI: 10.1016/j.phrs.2012.07.004

[210] Zhang YB, Gong JL, Xing TY, Zheng SP, Ding W. Autophagy protein p62/SQSTM1 is involved in HAMLET-induced cell death by modulating apotosis in U87MG cells. Cell Death & Disease. 2013;**4**:e550. DOI: 10.1038/cddis.2013.77

[211] Jin Z, Li Y, Pitti R, Lawrence D, Pham VC, Lill JR, et al. Cullin3-based polyubiquitination and p62-dependent aggregation of caspase-8 mediate extrinsic apoptosis signaling. Cell. 2009;**137**(4):721-735. DOI: 10.1016/j.cell.2009.03.015

[212] Khan SH, Zhao D, Shah SZ, Hassan MF, Zhu T, Song Z, et al. Parkin overexpression ameliorates PrP106-126-induced neurotoxicity via enhanced autophagy in N2a cells. Cellular and Molecular Neurobiology. 2017;**37**(4):717-728. DOI: 10.1007/s10571-016-0407-7

[213] Homma T, Ishibashi D, Nakagaki T, Satoh K, Sano K, Atarashi R, et al. Increased expression of p62/SQSTM1 in prion diseases and its association with pathogenic prion protein. Scientific Reports. 2014;**4**:4504. DOI: 10.1038/srep04504

[214] Katsuragi Y, Ichimura Y, Komatsu M. Regulation of the Keap1–Nrf2

pathway by p62/SQSTM1. Current Opinion in Toxicology. 2016;**1**:54-61. DOI: 10.1016/j.cotox.2016.09.005

[215] Caccamo A, Ferreira E, Branca C, Oddo S. p62 improves AD-like pathology by increasing autophagy. Molecular Psychiatry. 2017;**22**(6): 865-873. DOI: 10.1038/mp.2016.139

[216] Carroll JA, Race B, Williams K, Chesebro B. Toll-like receptor 2 confers partial neuroprotection during prion disease. PLoS One. 2018;**13**(12):e0208559. DOI: 10.1371/journal.pone.0208559

[217] Spinner DS, Cho IS, Park SY, Kim JI, Meeker HC, Ye X, et al. Accelerated prion disease pathogenesis in toll-like receptor 4 signaling-mutant mice. Journal of Virology. 2008;**82**(21):10701-10708. DOI: 10.1128/JVI.00522-08

[218] Walter S, Letiembre M, Liu Y, Heine H, Penke B, Hao W, et al. Role of the toll-like receptor 4 in neuroinflammation in Alzheimer's disease. Cellular Physiology and Biochemistry. 2007;**20**(6):947-956. DOI: 10.1159/000110455

[219] Minoretti P, Gazzaruso C, Vito CD, Emanuele E, Bianchi M, Coen E, et al. Effect of the functional toll-like receptor 4 Asp299Gly polymorphism on susceptibility to late-onset Alzheimer's disease. Neuroscience Letters. 2006;**391**(3):147-149. DOI: 10.1016/j.neulet.2005.08.047

[220] Reed-Geaghan EG, Savage JC, Hise AG, Landreth GE. CD14 and toll-like receptors 2 and 4 are required for fibrillar a{beta}-stimulated microglial activation. The Journal of Neuroscience. 2009;**29**(38):11982-11992. DOI: 10.1523/JNEUROSCI.3158-09.2009

[221] Lotz M, Ebert S, Esselmann H, Iliev AI, Prinz M, Wiazewicz N, et al. Amyloid beta peptide 1-40 enhances the action of toll-like receptor-2 and -4 agonists but antagonizes toll-like receptor-9-induced inflammation in primary mouse microglial cell cultures. Journal of Neurochemistry. 2005;**94**(2):289-298. DOI: 10.1111/j.1471-4159.2005.03188.x

[222] Tahara K, Kim HD, Jin JJ, Maxwell JA, Li L, Fukuchi K. Role of toll-like receptor signalling in Abeta uptake and clearance. Brain. 2006;**129**(Pt 11): 3006-3019. DOI: 10.1093/brain/awl249

[223] Tang SC, Lathia JD, Selvaraj PK, Jo DG, Mughal MR, Cheng A, et al. Toll-like receptor-4 mediates neuronal apoptosis induced by amyloid beta-peptide and the membrane lipid peroxidation product 4-hydroxynonenal. Experimental Neurology. 2008;**213**(1):114-121. DOI: 10.1016/j.expneurol.2008.05.014

[224] Calvo-Rodriguez M, de la Fuente C, Garcia-Durillo M, Garcia-Rodriguez C, Villalobos C, Nunez L. Aging and amyloid beta oligomers enhance TLR4 expression, LPS-induced Ca(2+) responses, and neuron cell death in cultured rat hippocampal neurons. Journal of Neuroinflammation. 2017;**14**(1):24. DOI: 10.1186/s12974-017-0802-0

[225] Gasic-Milenkovic J, Dukic-Stefanovic S, Deuther-Conrad W, Gartner U, Munch G. Beta-amyloid peptide potentiates inflammatory responses induced by lipopolysaccharide, interferon-gamma and "advanced glycation 'endproducts' in a murine microglia cell line. The European Journal of Neuroscience. 2003;**17**(4):813-821

[226] Perez-Pardo P, Dodiya HB, Engen PA, Forsyth CB, Huschens AM, Shaikh M, et al. Role of TLR4 in the gut-brain axis in Parkinson's disease: A translational study from men to mice. Gut. 2018;**68**:829-843. DOI: 10.1136/gutjnl-2018-316844

[227] Perez-Pardo P, Dodiya HB, Broersen LM, Douna H, van Wijk N,

Lopes da Silva S, et al. Gut-brain and brain-gut axis in Parkinson's disease models: Effects of a uridine and fish oil diet. Nutritional Neuroscience. 2018;**21**(6):391-402. DOI: 10.1080/1028415X.2017.1294555

[228] Pan-Montojo F, Anichtchik O, Dening Y, Knels L, Pursche S, Jung R, et al. Progression of Parkinson's disease pathology is reproduced by intragastric administration of rotenone in mice. PLoS One. 2010;**5**(1):e8762. DOI: 10.1371/journal.pone.0008762

[229] Drolet RE, Cannon JR, Montero L, Greenamyre JT. Chronic rotenone exposure reproduces Parkinson's disease gastrointestinal neuropathology. Neurobiology of Disease. 2009;**36**(1): 96-102. DOI: 10.1016/j.nbd.2009.06.017

[230] Clairembault T, Leclair-Visonneau L, Neunlist M, Derkinderen P. Enteric glial cells: New players in Parkinson's disease? Movement Disorders. 2015;**30**(4): 494-498. DOI: 10.1002/mds.25979

[231] Stefanova N, Reindl M, Neumann M, Kahle PJ, Poewe W, Wenning GK. Microglial activation mediates neurodegeneration related to oligodendroglial alpha-synucleinopathy: Implications for multiple system atrophy. Movement Disorders. 2007;**22**(15): 2196-2203. DOI: 10.1002/mds.21671

[232] Drouin-Ouellet J, St-Amour I, Saint-Pierre M, Lamontagne-Proulx J, Kriz J, Barker RA, et al. Toll-like receptor expression in the blood and brain of patients and a mouse model of Parkinson's disease. The International Journal of Neuropsychopharmacology. 2014;**18**(6):1-11. DOI: 10.1093/ijnp/pyu103

[233] Stefanova N, Fellner L, Reindl M, Masliah E, Poewe W, Wenning GK. Toll-like receptor 4 promotes alpha-synuclein clearance and survival of nigral dopaminergic neurons. The American Journal of Pathology. 2011;**179**(2):954-963. DOI: 10.1016/j.ajpath.2011.04.013

[234] Rietdijk CD, Van Wezel RJA, Garssen J, Kraneveld AD. Neuronal toll-like receptors and neuro-immunity in Parkinson's disease, Alzheimer's disease and stroke. Neuroimmunology and Neuroinflammation. 2016;**3**(2):27-37. DOI: 10.20517/2347-8659.2015.28

[235] Heiseke A, Aguib Y, Schatzl HM. Autophagy, prion infection and their mutual interactions. Current Issues in Molecular Biology. 2010;**12**(2):87-97

[236] Ravikumar B, Sarkar S, Davies JE, Futter M, Garcia-Arencibia M, Green-Thompson ZW, et al. Regulation of mammalian autophagy in physiology and pathophysiology. Physiological Reviews. 2010;**90**(4):1383-1435. DOI: 10.1152/physrev.00030.2009

[237] Martinez-Vicente M. Autophagy in neurodegenerative diseases: From pathogenic dysfunction to therapeutic modulation. Seminars in Cell & Developmental Biology. 2015;**40**:115-126. DOI: 10.1016/j.semcdb.2015.03.005

[238] Menzies FM, Fleming A, Caricasole A, Bento CF, Andrews SP, Ashkenazi A, et al. Autophagy and neurodegeneration: Pathogenic mechanisms and therapeutic opportunities. Neuron. 2017;**93**(5): 1015-1034. DOI: 10.1016/j.neuron.2017.01.022

[239] Heitz S, Grant NJ, Bailly Y. Doppel induces autophagic stress in prion protein-deficient Purkinje cells. Autophagy. 2009;**5**(3):422-424

[240] Heitz S, Grant NJ, Leschiera R, Haeberle AM, Demais V, Bombarde G, et al. Autophagy and cell death of Purkinje cells overexpressing Doppel in Ngsk Prnp-deficient mice. Brain Pathology. 2010;**20**(1):119-132. DOI: 10.1111/j.1750-3639.2008.00245.x

[241] Ma Y, Shi Q, Xiao K, Wang J, Chen C, Gao LP, et al. Stimulations of the culture medium of activated microglia and TNF-alpha on a

scrapie-infected cell line decrease the cell viability and induce marked necroptosis that also occurs in the brains from the patients of human prion diseases. ACS Chemical Neuroscience. 2018;**10**:1273-1283. DOI: 10.1021/acschemneuro.8b00354

[242] Wu HJ, Pu JL, Krafft PR, Zhang JM, Chen S. The molecular mechanisms between autophagy and apoptosis: Potential role in central nervous system disorders. Cellular and Molecular Neurobiology. 2015;**35**(1):85-99. DOI: 10.1007/s10571-014-0116-z

[243] Forbes JM, Thorburn DR. Mitochondrial dysfunction in diabetic kidney disease. Nature Reviews. Nephrology. 2018;**14**(5):291-312. DOI: 10.1038/nrneph.2018.9

[244] Szeto HH, Birk AV. Serendipity and the discovery of novel compounds that restore mitochondrial plasticity. Clinical Pharmacology and Therapeutics. 2014;**96**(6):672-683. DOI: 10.1038/clpt.2014.174

[245] Moussaoui S, Obinu MC, Daniel N, Reibaud M, Blanchard V, Imperato A. The antioxidant ebselen prevents neurotoxicity and clinical symptoms in a primate model of Parkinson's disease. Experimental Neurology. 2000;**166**(2):235-245. DOI: 10.1006/exnr.2000.7516

[246] Horvath TL, Diano S, Leranth C, Garcia-Segura LM, Cowley MA, Shanabrough M, et al. Coenzyme Q induces nigral mitochondrial uncoupling and prevents dopamine cell loss in a primate model of Parkinson's disease. Endocrinology. 2003;**144**(7):2757-2760. DOI: 10.1210/en.2003-0163

[247] Levites Y, Weinreb O, Maor G, Youdim MB, Mandel S. Green tea polyphenol (−)-epigallocatechin-3-gallate prevents N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced dopaminergic neurodegeneration. Journal of Neurochemistry. 2001;**78**(5):1073-1082

[248] Karunakaran S, Diwakar L, Saeed U, Agarwal V, Ramakrishnan S, Iyengar S, et al. Activation of apoptosis signal regulating kinase 1 (ASK1) and translocation of death-associated protein, Daxx, in substantia nigra pars compacta in a mouse model of Parkinson's disease: Protection by alpha-lipoic acid. The FASEB Journal. 2007;**21**(9):2226-2236. DOI: 10.1096/fj.06-7580com

[249] Kwon HJ, Cha MY, Kim D, Kim DK, Soh M, Shin K, et al. Mitochondria-targeting ceria nanoparticles as antioxidants for Alzheimer's disease. ACS Nano. 2016;**10**(2):2860-2870. DOI: 10.1021/acsnano.5b08045

[250] Sweeney G, Song J. The association between PGC-1alpha and Alzheimer's disease. Anatomy & Cell Biology. 2016;**49**(1):1-6. DOI: 10.5115/acb.2016.49.1.1

[251] Cortes CJ, Qin K, Cook J, Solanki A, Mastrianni JA. Rapamycin delays disease onset and prevents PrP plaque deposition in a mouse model of Gerstmann-Straussler-Scheinker disease. The Journal of Neuroscience. 2012;**32**(36):12396-12405. DOI: 10.1523/JNEUROSCI.6189-11.2012

[252] Jiang T, Yu JT, Zhu XC, Tan MS, Wang HF, Cao L, et al. Temsirolimus promotes autophagic clearance of amyloid-beta and provides protective effects in cellular and animal models of Alzheimer's disease. Pharmacological Research. 2014;**81**:54-63. DOI: 10.1016/j.phrs.2014.02.008

[253] Menzies FM, Huebener J, Renna M, Bonin M, Riess O, Rubinsztein DC. Autophagy induction reduces mutant ataxin-3 levels and toxicity in a mouse model of spinocerebellar ataxia type 3. Brain. 2010;**133**(Pt 1):93-104. DOI: 10.1093/brain/awp292

[254] Ozcelik S, Fraser G, Castets P, Schaeffer V, Skachokova Z, Breu K, et al. Rapamycin attenuates the progression of tau pathology in P301S tau transgenic mice. PLoS One. 2013;**8**(5):e62459. DOI: 10.1371/journal.pone.0062459

[255] Ravikumar B, Vacher C, Berger Z, Davies JE, Luo S, Oroz LG, et al. Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. Nature Genetics. 2004;**36**(6):585-595. DOI: 10.1038/ng1362

[256] Sarkar S, Krishna G, Imarisio S, Saiki S, O'Kane CJ, Rubinsztein DC. A rational mechanism for combination treatment of Huntington's disease using lithium and rapamycin. Human Molecular Genetics. 2008;**17**(2):170-178. DOI: 10.1093/hmg/ddm294

[257] Spilman P, Podlutskaya N, Hart MJ, Debnath J, Gorostiza O, Bredesen D, et al. Inhibition of mTOR by rapamycin abolishes cognitive deficits and reduces amyloid-beta levels in a mouse model of Alzheimer's disease. PLoS One. 2010;**5**(4):e9979. DOI: 10.1371/journal.pone.0009979

[258] Wang IF, Tsai KJ, Shen CK. Autophagy activation ameliorates neuronal pathogenesis of FTLD-U mice: A new light for treatment of TARDBP/TDP-43 proteinopathies. Autophagy. 2013;**9**(2):239-240. DOI: 10.4161/auto.22526

[259] DeBosch BJ, Heitmeier MR, Mayer AL, Higgins CB, Crowley JR, Kraft TE, et al. Trehalose inhibits solute carrier 2A (SLC2A) proteins to induce autophagy and prevent hepatic steatosis. Science Signaling. 2016;**9**(416):ra21. DOI: 10.1126/scisignal.aac5472

[260] Aguib Y, Heiseke A, Gilch S, Riemer C, Baier M, Schatzl HM, et al. Autophagy induction by trehalose counteracts cellular prion infection. Autophagy. 2009;**5**(3):361-369

[261] Chen L, Xie Z, Turkson S, Zhuang X. A53T human alpha-synuclein overexpression in transgenic mice induces pervasive mitochondria macroautophagy defects preceding dopamine neuron degeneration. The Journal of Neuroscience. 2015;**35**(3):890-905. DOI: 10.1523/JNEUROSCI.0089-14.2015

[262] Du J, Liang Y, Xu F, Sun B, Wang Z. Trehalose rescues Alzheimer's disease phenotypes in APP/PS1 transgenic mice. The Journal of Pharmacy and Pharmacology. 2013;**65**(12):1753-1756. DOI: 10.1111/jphp.12108

[263] Rodriguez-Navarro JA, Rodriguez L, Casarejos MJ, Solano RM, Gomez A, Perucho J, et al. Trehalose ameliorates dopaminergic and tau pathology in parkin deleted/tau overexpressing mice through autophagy activation. Neurobiology of Disease. 2010;**39**(3):423-438. DOI: 10.1016/j.nbd.2010.05.014

[264] Schaeffer V, Goedert M. Stimulation of autophagy is neuroprotective in a mouse model of human tauopathy. Autophagy. 2012;**8**(11):1686-1687. DOI: 10.4161/auto.21488

[265] Tanji K, Miki Y, Maruyama A, Mimura J, Matsumiya T, Mori F, et al. Trehalose intake induces chaperone molecules along with autophagy in a mouse model of Lewy body disease. Biochemical and Biophysical Research Communications. 2015;**465**(4):746-752. DOI: 10.1016/j.bbrc.2015.08.076

[266] Ledo JH, Azevedo EP, Beckman D, Ribeiro FC, Santos LE, Razolli DS, et al. Cross talk between brain innate immunity and serotonin signaling underlies depressive-like behavior induced by Alzheimer's amyloid-beta oligomers in mice. The Journal of

Neuroscience. 2016;**36**(48):12106-12116. DOI: 10.1523/JNEUROSCI.1269-16.2016

[267] Lourenco MV, Clarke JR, Frozza RL, Bomfim TR, Forny-Germano L, Batista AF, et al. TNF-alpha mediates PKR-dependent memory impairment and brain IRS-1 inhibition induced by Alzheimer's beta-amyloid oligomers in mice and monkeys. Cell Metabolism. 2013;**18**(6):831-843. DOI: 10.1016/j.cmet.2013.11.002