



Autophagy and apoptosis dysfunction in neurodegenerative disorders



Saeid Ghavami ^{a,b,c,1}, Shahla Shojaei ^{d,1}, Behzad Yeganeh ^{b,l,1}, Sudharsana R. Ande ^e, Jaganmohan R. Jangamreddy ^f, Maryam Mehrpour ^g, Jonas Christoffersson ^f, Wiem Chaabane ^{f,h}, Adel Rezaei Moghadam ⁱ, Hessam H. Kashani ^{a,b}, Mohammad Hashemi ^{j,k}, Ali A. Owji ^{d,2,**}, Marek J. Łos ^{f,2,*}

^a Department of Human Anatomy and Cell Science, University of Manitoba, Winnipeg, Canada

^b Manitoba Institute of Child Health, Department of Physiology, University of Manitoba, Winnipeg, Canada

^c St. Boniface Research Centre, University of Manitoba, Winnipeg, Canada

^d Department of Biochemistry, Recombinant Protein Laboratory, Medical School, Shiraz University of Medical Sciences, Shiraz, Iran

^e Department of Internal Medicine, University of Manitoba, Winnipeg, Canada

^f Department of Clinical and Experimental Medicine (IKE), Integrative Regenerative Medicine Center (IGEN), Division of Cell Biology, Linköping University, Linköping, Sweden

^g INSERM U845, Research Center "Growth & Signaling" Paris Descartes University Medical School, France

^h Department of Biology, Faculty of Sciences, Tunis University, Tunis, Tunisia

ⁱ Young Researchers Club, Ardabil Branch, Islamic Azad University, Ardabil, Iran

^j Department of Clinical Biochemistry, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran

^k Cellular and Molecular Biology Research Center, Zahedan University of Medical Sciences, Zahedan, Iran

¹ Hospital for Sick Children Research Institute, Department of Physiology and Experimental Medicine, University of Toronto, Canada

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ABSTRACT

Autophagy and apoptosis are basic physiologic processes contributing to the maintenance of cellular homeostasis. Autophagy encompasses pathways that target long-lived cytosolic proteins and damaged organelles. It involves a sequential set of events including double membrane formation, elongation, vesicle maturation and finally delivery of the targeted materials to the lysosome. Apoptotic cell death is best described through its morphology. It is characterized by cell rounding, membrane blebbing, cytoskeletal collapse, cytoplasmic condensation, and fragmentation, nuclear pyknosis, chromatin condensation/fragmentation, and formation of membrane-enveloped apoptotic bodies, that are rapidly phagocytosed by macrophages or neighboring cells. Neurodegenerative disorders are becoming increasingly prevalent, especially in the Western societies, with larger percentage of members living to an older age. They have to be seen not only as a health problem, but since they are care-intensive, they also carry a significant economic burden. Deregulation of autophagy plays a pivotal role in the etiology and/or progress of many of these diseases. Herein, we briefly review the latest findings that indicate the involvement of autophagy in neurodegenerative diseases. We provide a brief introduction to autophagy and apoptosis pathways focusing on the role of mitochondria and lysosomes. We then briefly highlight pathophysiology of common neurodegenerative disorders like Alzheimer's diseases, Parkinson's disease, Huntington's disease and Amyotrophic lateral sclerosis. Then, we describe functions of autophagy and

Abbreviations: AMBRA, activating molecule in Beclin-1-regulated autophagy; AD, Alzheimer's diseases; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; A β , amyloid-beta; α -syn, alpha-synuclein; ALS, amyotrophic lateral sclerosis; APP, amyloid beta precursor protein; AMPK, AMP-activated protein kinase; Apo-E, apolipo-protein E; AIF, apoptosis-inducing factor; ATG, autophagy related genes; LC3, autophagosome-associated light chain 3; BDNF, brain-derived neurotrophic factor; CMA, chaperon-mediated autophagy; ER, endoplasmic reticulum; ESCRT, endosomal sorting complexes required for transport; HEK293, human embryonic kidney 293 cells; HD, Huntington's disease; Htt, Huntingtin protein; HIP-1, Huntington interacting protein; InsP(6)Ks, inositol hexakisphosphate kinases; LAMP, lysosomal associated membrane proteins; MAP15, microtubule-associated protein 15; LRRK2, mitochrondrially-associated leucine-rich PPR-motif containing protein; mPTP, mitochondrial permeability transition pore; mTOR, mammalian target of rapamycin; mHtt, mutant Huntingtin protein; NMDA, N-methyl-D-aspartate; NCCD, nomenclature committee on cell death; PD, Parkinson's disease; PON 1–3, paraxonase enzymes; pQ, poly-glutamine; PCD, programmed cell death; PINK-1, PTEN-induced putative kinase 1; RCAN-1, regulator of calcineurin-1; RUBICON, RUN domain and cysteine rich domain containing; TDP-43-kDa, TAR DNA-binding protein 43 kDa; p53, tumor protein 53; UPS, ubiquitin-proteasome system; UVAG, ultra-violet radiation resistance-associated gene; VCP, valosin-containing protein; XBP-1, X-box binding protein-1.

* Corresponding author. Tel.: +46 101032787.

** Corresponding author.

E-mail addresses: aaoowji@yahoo.com (A.A. Owji), mjelos@gmail.com (M.J. Łos).

¹ All three authors have equal first authorship.

² Both authors have equal senior authorship.

apoptosis in brain homeostasis, especially in the context of the aforementioned disorders. Finally, we discuss different ways that autophagy and apoptosis modulation may be employed for therapeutic intervention during the maintenance of neurodegenerative disorders.

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Contents

1. Introduction	25
2. Cell death	26
3. Autophagy	26
4. Autophagy machinery and its regulation	26
5. Role of mitochondria in autophagy	27
6. Autophagy and brain homeostasis	28
7. Apoptosis and its regulation	29
8. Importance of apoptosis in central- and peripheral nerve system	30
9. Alzheimer's disease	30
10. Parkinson's disease	31
11. Huntington's disease	32
12. Amyotrophic lateral sclerosis	32
13. Neuroinflammation in neurodegenerative diseases	32
13.1. General dynamics of neuroinflammation in neurodegenerative diseases	32
13.2. Alzheimer's diseases and neuroinflammation	32
13.3. Parkinson's disease and neuroinflammation	33
13.4. Amyotrophic lateral sclerosis and neuroinflammation	33
14. Autophagy hyperactivation or failure associated with neuronal cell death	33
15. Autophagy and neurodegenerative disease	35
15.1. Alzheimer's diseases – disturbed autophagy as a contributing factor	35
15.2. Parkinson's disease – autophagy as possible protective factor	35
15.3. Huntington's disease – potential pro-survival effect of autophagy	36
15.4. Convoluted role of autophagy in the etiology and progression of amyotrophic lateral sclerosis	36
15.5. Autophagy and neuroinflammation	37
16. Apoptosis and neurodegenerative disease	37
16.1. Apoptosis in Alzheimer's diseases	37
16.2. The role of apoptosis in the etiology and progression of Parkinson's disease	37
16.3. Excitotoxicity-triggered apoptosis and other effects of mutated huntingtin protein in Huntington's disease	38
16.4. Amyotrophic lateral sclerosis and the role of apoptosis in the onset and progression of the disease	38
17. Connection between age-related neurodegenerative disorders and cell aging/cell senescence	39
18. The potential of autophagy- and apoptosis modulation as a treatment strategy in neurodegenerative diseases	39
18.1. Autophagy modulation and Huntington's diseases treatment strategies	39
18.2. Alzheimer's diseases – autophagy modulation as therapy approach	40
18.3. Parkinson's disease – therapeutic effect of autophagy	41
18.4. Apoptosis modulation and neurodegenerative diseases treatment strategy	41
19. Closing remarks	42
Acknowledgements	42
References	42

1. Introduction

In proteopathies, certain proteins become structurally abnormal, accumulate in cells and tissues, and disrupt their function (Luheshi et al., 2008). Proteopathies include diverse neurodegenerative disorders such as Alzheimer's diseases (AD), Parkinson's disease (PD), Huntington's disease (HD) and Amyotrophic lateral sclerosis (ALS) in which abnormally assembled proteins appear to play a central role (Xilouri and Stefanis, 2010). Abnormal or misfolded proteins, when aggregated in cytoplasmic, nuclear and extracellular inclusions cause organelle damage and synaptic dysfunction in the nervous system (Walker and LeVine, 2000). Two elimination pathways are currently known for damaged cellular components. Both of them control the quality of cellular components and maintain cell homeostasis. These are, the ubiquitin-proteasome system (UPS) that degrades short-lived proteins in the cytoplasm and nucleus, and the autophagy-lysosome pathway (ALP) which digests long-lived proteins and abnormal organelles just in the cytoplasm (Nijholt et al., 2011). The proper function and balance in the action of these two systems are

especially important in neurons and other long-lived cells. Hence, their dysfunction contributes to pathogeneses of neurodegenerative diseases (Ciechanover, 2005; Rubinsztein, 2006).

Besides autophagy disturbances, deregulation of apoptosis is associated with a long list of pathologies, including neurodegenerative disorders (Agostini et al., 2011). After multi-cellular organisms reach adulthood, apoptotic processes remove old and damaged cells to maintain tissue homeostasis without harming adjacent cells (Hellwig et al., 2011). With the exception of post-mitotic cells such as differentiated neurons and muscle cells, which are usually highly apoptosis-resistant, the majority of other cells in the body is regularly renewed, particularly within epithelia, endothelia and the blood (Hellwig et al., 2011). Hence, recent reports have emphasized the importance of apoptosis in proteopathies diseases (Agostini et al., 2011; Hellwig et al., 2011).

Below, we briefly introduce autophagy and apoptosis pathways focusing on the role of mitochondria and lysosomes in both pathways, followed by autophagy and apoptosis function in brain homeostasis. Furthermore, some of the most common neurodegenerative diseases will be described, then, we explain characteristic

features of macroautophagy and apoptosis. Finally, their significance in the pathogenesis of neurodegenerative diseases as well as potential therapeutic modulators of these pathways and their applications in neurodegenerative diseases are highlighted.

2. Cell death

The discovery of cell-embedded mechanism of cell death pathways in the 20th century lead to the dissolution of more than a century old notions that the natural death is a passive process (Surova and Zhivotovsky, 2012). Apoptosis and necroptosis are among major cell death mechanisms and are known as programmed cell death pathways (PCD) (Lee et al., 2012). Necroptosis resembles initial apoptotic phenotype, which later on, it propagated by necrotic cell death machinery (Lee et al., 2012). Necrotic response was first reported at least a quarter of a century earlier than apoptosis, is thought to be due to sudden and drastic stress (Mughal et al., 2012). Cell swelling, rupture of the cell membrane and thus triggering inflammation in the surrounding cell milieu characterize necrotic cell death (Galluzzi et al., 2011). However, recent findings suggest that at least in some instances necrotic cell death is regulated, and is triggered by specific kinase (RIP1 and 3 kinase) pathways, and inhibited by necrostatin1 (Cho et al., 2009; Holler et al., 2000; Vandenabeele et al., 2010). Moreover, like apoptosis, necroptosis and autophagy, both are also involved in homeostasis and embryonic development. Furthermore, at least some cell death stimuli activate both necrotic and apoptotic pathway and necrosis becomes visible only if the apoptotic pathway, that acts faster, is blocked (Los et al., 2002). In addition, some stimuli may trigger mitochondrial degeneration called mitoptosis (Jangamreddy and Los, 2012) that in turn may promote cell death via hyper-autophagy.

3. Autophagy

Autophagy (derived from the Greek words for “self” and “eating”), the word by discernment and interpretation comes across as a self-sacrificing mechanism, which has important role in cell fate as well as maintaining cell metabolic balance (Eisenberg-Lerner et al., 2009). For decades, autophagy has been debated as an active cell death pathway while recently cell survival function of this pathway has been underlined. Along with previous developmental studies, more recent data support autophagy-induced caspase-dependent and independent cell death. However, many unanswered questions remain regarding the interconnecting regulators of apoptosis and autophagy (Berry and Baehrecke, 2007). Regardless of the controversies, at basal levels autophagy plays vital role in keeping the cell homeostasis by digestion of dysfunctional organelles and proteins (Mizushima, 2007). Defective autophagy pathway or alterations in autophagy-related genes is shown in various human pathologies including neurodegenerative and lysosomal storage disorders as well as in various cancers (Mizushima et al., 2008; Ravikumar et al., 2010).

As mentioned in the previous section, autophagy includes three major types: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). Pathways that lead to organelle-specific autophagy (Mitophagy, Ribophagy, Pexophagy, etc.) have also been recently described (Manjithaya et al., 2010; Suzuki, 2013; Trempe and Fon, 2013). The characterization of these pathways, however, is at the relatively early stages. Macroautophagy (hereafter called autophagy) is a conserved pathway in eukaryotic cells that enables the bulk degradation of cytoplasmic components. The target components are sequestered within double-membrane vesicle named autophagosome, which are then transported to the lysosome for degradation, whereas microautophagy is a process that require direct uptake and degradation

of cytoplasm by lysosomes, without the involvement of intermediate transport vesicles (Glick et al., 2010). CMA can be distinguished from macro- and microautophagy by its requirement for the presence of a consensus pentapeptide sequence, LysPheGluArgGln, in the substrate protein (SP). The heat shock proteins (HSP70, a cytosolic chaperone protein) binds to the SP, and the pentapeptide sequence of the substrate-chaperone complex are recognized by LAMP2A, the lysosomal CMA receptor. The SP is the unfolded and translocated across the lysosomal membrane and is degraded in the lysosome (Cuervo, 2011).

4. Autophagy machinery and its regulation

Autophagy is evolutionarily well conserved from early eukaryotes to mammals with as many as 30 Autophagy related genes (ATGs) identified in yeasts, and their human orthologs. Autophagic process involving the ATGs is majorly regulated through mTOR (mammalian target of rapamycin), which under physiological conditions inhibits the autophagy by restraining the kinase activity of ULK (Ubiquitin like Kinase) (Glick et al., 2010). Autophagic vesicle formation involves initiation, elongation and maturation steps with subsequent fusion with lysosomes to form autolysosome or amphisome (Alavian et al., 2011; Glick et al., 2010). In mammals, the details of the initial pre-autosomal complex formation are still not clear. However, the process includes the de novo formation of initiation complex consisting of ULK complex with ATG1, ATG13, ATG17 and ATG9, regulatory class III PI3 kinase complex with beclin-1 (also known as ATG6) and ATG5-ATG12-ATG16 multimerization complex (Kabeya et al., 2005; Mizushima, 2010). ATG1-ATG13 complex recruits ATG9, a transmembrane protein ATG9, which is crucial for the initial lipidation of the phagophore membrane (Ravikumar et al., 2010). PI3 kinase-beclin-1 complex depending on the interaction partners can activate or repress autophagy and also recruit other ATG proteins that are crucial for the development of the phagosome. UVRAG (Ultra-Violet Radiation Resistance-Associated Gene) when associated with AMBRA (Activating molecule in beclin-1-regulated autophagy) and ATG14 promote autophagy through beclin-1 complex interaction (Liang et al., 2006). On the other hand, UVRAG complexed with RUBICON (RUN domain and cysteine rich domain containing) interaction leads to autophagy repression (Matsunaga et al., 2009).

Upon autophagy stimulation, beclin-1 is released from Bcl2 at the endoplasmic reticulum, forms complex with UVRAG/AMBRA, triggering ATG5-ATG12-ATG16 multimeric complex formation mediated by ATG7 and ATG10 (Glick et al., 2010). Thus formed initiating membrane is further incorporated with LC3 β II, which is a cleaved and lipidated product of LC3 β I (ATG8) by ATG4 and later conjugated with phosphatidylethanolamine (PE), irregularly on both sides of the membrane by ATG9 of the ULK complex (Ghavami et al., 2012a). During further elongation and autophagosome formation around the selected cargo for degradation, recruitment of the membrane from endoplasmic reticulum, mitochondria and at times even nuclear membrane is well documented (Axe et al., 2008; Hailey et al., 2010). The completion of autophagosome is marked by the release of LC3 β II from the exterior surface of the membrane, which is then recycled. Thus, LC3 β II is a prominent marker to monitor autophagic flux (Glick et al., 2010; Gong et al., 2012). The newly formed autophagosome along with the cargo to be degraded fuses with lysosome to form autophagolysosome or autolysosome. The transient formation of amphisome provides the necessary pH required for the optimal activity of lysosomal proteases. The fusion of the lysosome with autophagosome is facilitated by cytoskeletal microtubules by transferring the autophagosomes to lysosomal proximity for lysosomal membrane proteins LAMP1/2 and Rab7, member of Rab family GTPases and

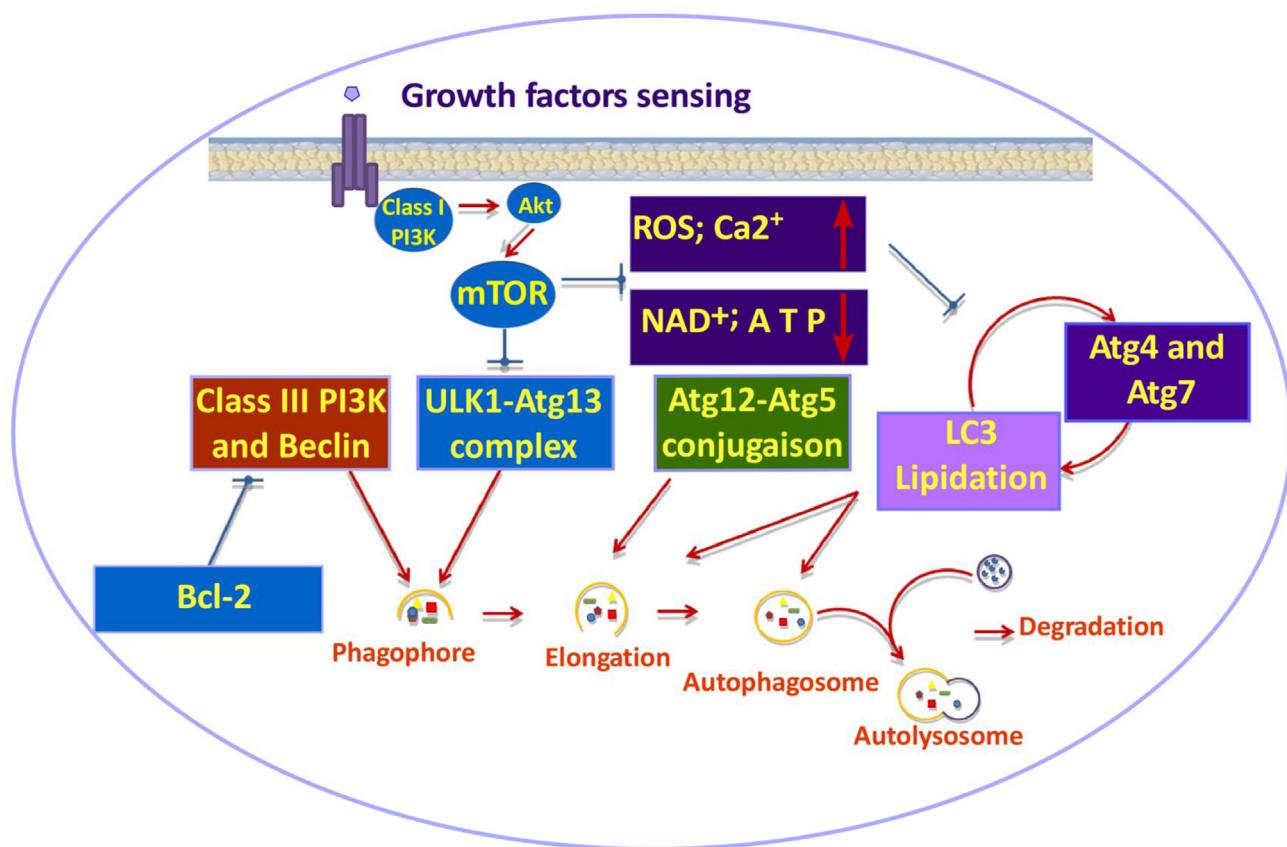


Fig. 1. Summary of basic autophagy signaling events. The key regulator of autophagy, mTOR, is inhibited in the course of multiple metabolically stressful events, including deprivation of nutrients or growth factors from the extracellular milieu. mTOR directly phosphorylates ULK1 and mAtg13 and inhibits ULK1 kinase activity, which is essential for autophagy induction. Thus, autophagy is initiated by the nucleation of an isolation membrane or phagophore. This membrane then elongates and closes on itself to form an autophagosome. Growth factors, such as insulin, bind to membrane receptors to activate class I PI3K. This process generates PI(3,4,5)P₃, which recruits protein kinase B (PKB/Akt) and its activator PDK1 (phosphoinositide-dependent kinase 1) to the plasma membrane, resulting in activation of PKB/Akt. Active PKB/Akt indirectly activates mTOR through inhibition of negative regulators [tuberous sclerosis complex (TSC1/2)] of mTOR and activating the mTOR activator Rheb (Ras homolog enriched in brain). The Beclin-1 complex contributes to the nucleation of the phagophore. Beclin-1 complex is regulated by Bcl-2. Elongation of the phagophore membrane is dependent on the Atg12 and LC3 conjugation systems. Closure of the autophagosome is dependent on the activity of the LC3-conjugation system. The autophagosome matures by fusing with endosomes and lysosomes, finally forming the autolysosome where the cargo degradation occurs. Many stimuli that induce ROS generation also induce autophagy, including nutrient starvation, mitochondrial toxins, hypoxia, and oxidative stress (Jangamreddy et al., 2013). Recently, it was demonstrated that ROS might induce autophagy through several distinct mechanisms involving Atg4, catalase, and the mitochondrial electron transport chain (mETC). This leads to both cell-survival and cell-death responses.

vesicular proteins, class III Vps, SNARE and ESCRT to enable fusion (Atashkeni et al., 2003; Gutierrez et al., 2004b; Lee et al., 2007; Webb et al., 2004). The stages of autophagy pathway have been summarized in Fig. 1.

5. Role of mitochondria in autophagy

Mitochondria and their physical dynamics play a vital role at several stages of autophagy from initial biogenesis of autophagosome and regulation of the autophagy through beclin-1 to the autophagy-mediated cell death (Rubinstein et al., 2012). Recent studies show that the mitochondrial outer membrane recruits the autophagy proteins ATG5 and LC3. They are recruited not for the autophagic removal of mitochondria, mitophagy, but to provide the anchorage and share the lipid moieties required for the elongation of the initial phagophore. In the same study, they illustrate that the cells that lack the mitochondrial protein Mfn2, which mediate mitochondria anchoring to the endoplasmic reticulum, do not show such recruitment of ATG5 or LC3 in the vicinity. This observation suggesting the crucial role of mitochondria and endoplasmic reticulum in the initiation of autophagy (Hailey et al., 2010). Moreover, mitochondria form tubular structures by connecting to one another (mitochondrial fusion), during serum starvation, which also promptly induces autophagy

(Twig and Shirihai, 2011). However, the dysfunctional enlarged senescent mitochondria accumulated during the aging process, lack the ability to fuse and hamper autophagy (Barnett and Brewer, 2011).

Mitochondria also regulate autophagy through their proteins Bif1 and Sirt1 by interacting with autophagy initiation complexes (Kawashima et al., 2011; Takahashi et al., 2007, 2011). Bif1 (also present in Golgi complex) is mainly involved in endosome formation, also binds to positive regulator complex of autophagy, UVRAG and beclin-1, and promotes autophagy (Takahashi et al., 2007, 2008). Sirt1 promotes autophagy by directly interacting with ATG5, ATG7 and LC3/ATG8 (Lee et al., 2008). Other mitochondrial protein involved in induction of autophagy is smARF, short mitochondrial form of ARF tumor suppressor protein that induces cell cycle arrest through p53 dependent pathway, and type I programmed cell death (apoptosis) (Reef et al., 2006). Unlike its longer version, smARF induces excessive autophagy-mediated non-apoptotic cell death that can be counteracted by knockdown of ATG5 or beclin-1 (Reef et al., 2006).

Mitochondria play a prominent role in autophagy-mediated cell death by cytochrome c release, either mediated by cleaved products of ATG4 and ATG5, or through leaked lysosomal protease, triggered activation of phospholipases and Bax/Bak (Betin and Lane, 2009; Terman et al., 2010). Fig. 2 outlines mitochondria and

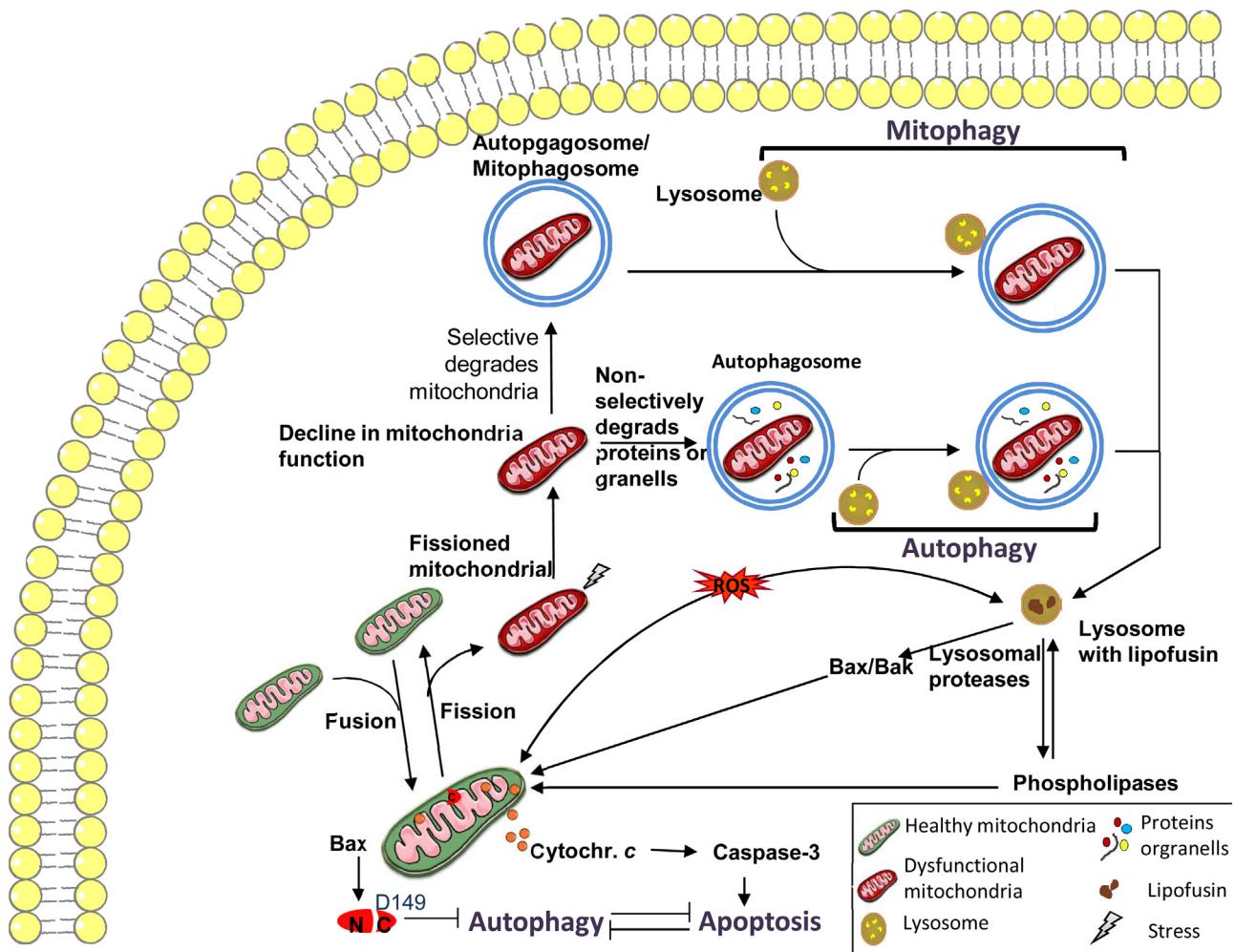


Fig. 2. Mitochondrial and lysosomal synergistic interplay during aging. Accumulation of non-degradable lipofuscin leads to vicious cyclic damage of mitochondria and lysosomes mediated by ROS. Apoptosis induced by the proapoptotic protein Bax reduced autophagy by enhancing caspase-mediated cleavage of beclin-1 at D149.

lysosomes interplay in autophagy, in the context of mitochondrial aging.

6. Autophagy and brain homeostasis

Neurons are differentiated cells with polarized cell-body. Their viability and function is closely connected to the availability of trophic factors (include for example neurotrophins like nerve growth factor (NGF), but also critically depends on active membrane transport connecting the distant cell body with dendrites and axons. Neurons, because of their extreme polarization, size and post-mitotic nature may be particularly sensitive to the accumulation of aggregated or damaged cytosolic compounds, or membranes, and depend on autophagy for survival (Tooze and Schiavo, 2008).

Thus, the beneficial roles of autophagy in nervous system are mainly associated with maintaining of the normal balance between the formation and degradation of cellular proteins as defects in autophagy pathway have been linked to neurodegenerative diseases, such as PD (Anglade et al., 1997), AD (Cataldo et al., 1996), HD (Kegel et al., 2000), and transmissible spongiform encephalopathy (prion disease) (Liberski et al., 2004). Although inclusion bodies characterize virtually all neurodegenerative diseases, they are different in origin and structure, thus causing disorders with different pathogenesis. In general, both macroautophagy and CMA, become markedly less-efficient during

normal aging, thus contributing directly toward declining of tissue performance (Martinez-Vicente et al., 2005). In neurodegenerative disorders, it is postulated that incomplete CMA of cytosolic proteins leads to generation of amyloidogenic fragments that promote aggregation, which subsequently needs to be removed by macroautophagy (Cuervo et al., 2004).

Because of bulk removal of intracellular aggregated proteins by macroautophagy, extensive efforts have been made to understand whether autophagy is activated to eliminate these aggregated proteins, or the existence of aggregates is attributed to malfunctioning of the autophagic pathway. On the other hand, there are studies suggesting that aggregates themselves might actually serve a neuroprotective function (Arrasate et al., 2004; Rubinsztein, 2006).

Mouse models that accurately model human disease serve as important research tools to elucidate the mechanisms underlying in progression of neurodegenerative disorders. Komatsu et al. (2006) generated mice with tissue-specific ATG7-knockdown in the CNS. These mice showed accumulation of inclusion body in autophagy-deficient neurons with no obvious alteration in proteasome function. Inclusion bodies were increasing in size and number with age leading to extensive neuronal loss and death within 28 weeks of birth. Their results strongly suggest that autophagy is essential for the survival of neural cells and that inadequate level of autophagy is implicated in the pathogenesis of neurodegenerative disorders involving ubiquitin-containing inclusions.

Alterations in macroautophagy pathway in pathogenesis of neurodegenerative diseases have been extensively studied over the past few years. Although these studies have made significant advances in our understanding of the defective steps that lead to dysfunction of this pathway during aging and age-related neurodegenerative disorders, most of the molecular components responsible for diminished autophagic activity associated with these diseases still remain elusive.

7. Apoptosis and its regulation

Apoptosis, as proposed by the nomenclature committee on cell death (NCCD), comprise rounding-up of the cell, shrinkage of pseudopods, decreased cellular volume, chromatin condensation (pyknosis), nuclear fragmentation (karyorrhexis) along with little or no ultrastructural reformations of organelles in cytoplasm followed by plasma membrane blebbing and ingestion by phagocytes (Los et al., 1999; Rashedi et al., 2007) (Fig. 3). Proteolytic enzymes with specificity toward aspartate, and with cysteine in their active center, called caspases, are well conserved from early nematodes to the modern vertebrates and are the main propagators of apoptotic program at the cellular level (Ghavami et al., 2009b; Stroh et al., 2002). Caspases are present in the cytoplasm as inactive forms (zymogens), and are activated by proteolysis (Ghavami et al., 2012c). Caspases have central functions in mammalian cell apoptosis. The role and indispensability of individual caspases in mammalian cell death have been best illustrated based on gene-knockout studies (Los et al., 1999).

Caspases are classified into two different groups based on the hierarchical role in action namely initiator and effector caspases. The initiator caspases (caspase-8 and caspase-9) are activated first by upstream signals (Los et al., 1995) which later on, activate the effector caspases (i.e. caspase-3 and caspase-7) (Fuchs and Steller, 2011; Ghavami et al., 2009b). The initiator caspases are activated by external cell death triggering molecules (for caspase-8: TRAIL, TNF α , Fas, etc.) (Hashemi et al., 2013; Los et al., 1995) and caspase-9 activation is triggered by internal stress (starvation and cellular dysfunction) leading to mitochondrial release of cytochrome c, which triggers the formation of the apoptosome complex (the caspase-9 activating complex) (Fuchs and Steller, 2011). Caspase-8 might cleave Bid molecule forming truncated Bid (t-Bid), which later promotes mitochondrial cytochrome c release and causes caspase-9 activation (Ghavami et al., 2009a).

Extrinsic apoptotic pathway acts fast (1–2 h under optimal conditions). Engaged receptors trimerize, recruit adaptor molecules to their death domains and trigger the activation of caspase-8, and subsequently caspase-3 and -7 that lead to cell death (Lakhan et al., 2006; Rashedi et al., 2007). In the case of intrinsic (mitochondrial) apoptotic pathway, a shift in the balance of pro-apoptotic Bcl2 family members (Bax, Bak, etc.) and anti-apoptotic member's toward pro-apoptotic ones, leads to their accumulation in the outer membrane of mitochondria (Fuchs and Steller, 2011; Ghavami et al., 2012b), thus leading to the formation of permeability transition pore (PTP), and subsequent cytochrome c release (Fig. 3). Cytochrome c and Apaf1 (Apoptotic protease-activating factor 1) form with pro-caspase-9 in the presence of

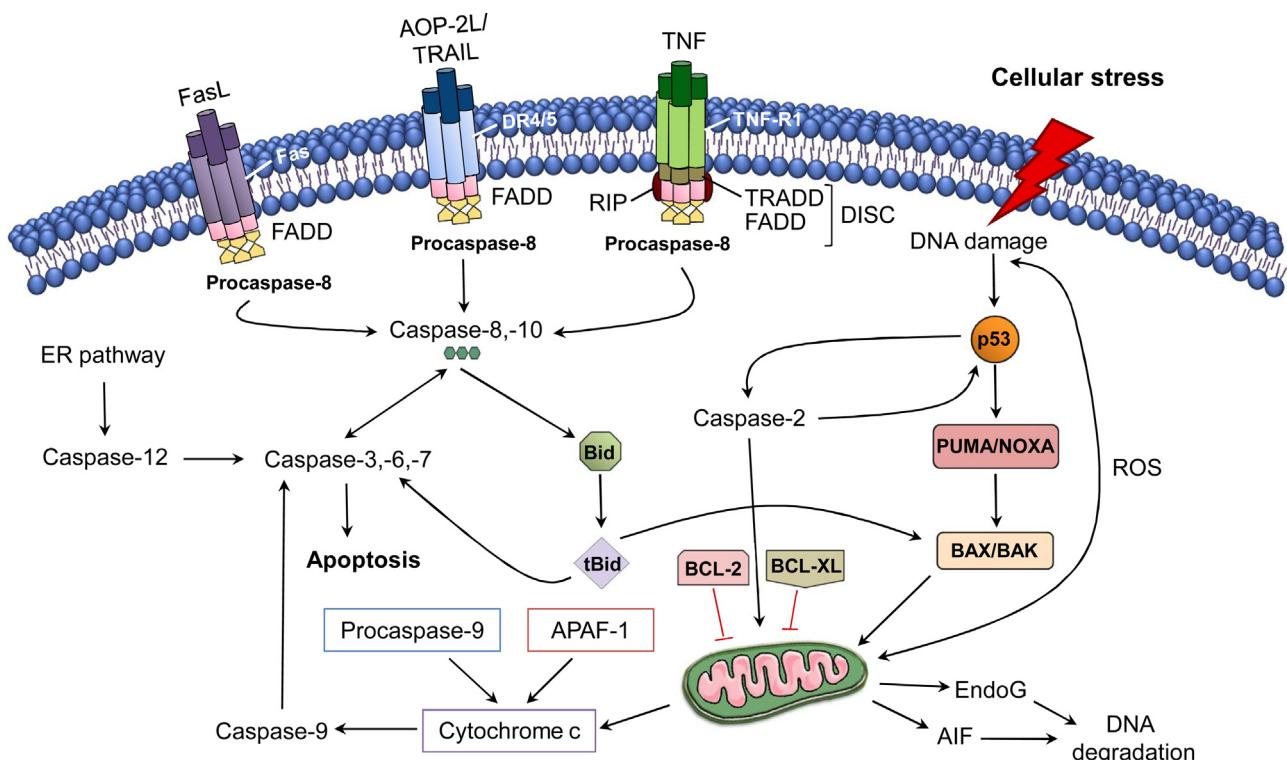


Fig. 3. Schematic representation of apoptotic pathways. Apoptosis triggered by internal (intrinsic) or external (extrinsic) stress signals that is activated by binding of ligands (e.g. FasL, APO-2L, TRAIL, TNF) to cell surface receptors (e.g. Fas, DR4, DR5, TNF-R1). The intrinsic apoptosis pathway might be triggered by p53 upon DNA damage following exposure to cellular stress. In the intrinsic pathway, death signal reaches mitochondria, leading to release of cytochrome c, which can binds to Apaf1. The cytochrome c/Apaf1 make a complex with pro-caspase-9 (in the presence of dATP), activates caspase-9, which promotes caspase-3 activation, eventually leading to cell death. The extrinsic pathway is initiated through the stimulation of the members of tumor necrosis factor receptor (TNF-R) family (transmembrane death receptors) by their respective ligands. These receptors activate pro-caspase-8, -10 by recruiting the endogenous adaptor protein FADD. Procaspsase-8, -10 cleave themselves to form activated caspase-8 or -10. Ultimately, effector enzymes such as caspase-3, -6, -7 are activated in this cascade to mediate apoptosis. Likewise, there can be cross-talk between the intrinsic and extrinsic pathways. For example caspase-8 may cleave Bid to form tBid that is a strong activator of the intrinsic/mitochondrial apoptotic pathway. The intrinsic pathway is usually activated by the recruitment of BAX and BAK to outer mitochondrial membrane, causing cytochrome c release formation of apoptosome and subsequent activation of caspase-9. Activated caspase-9 proteolytically activates caspases-3, -6, and -7. Moreover, some of the effector caspases also can activate caspase-8, forming a positive amplification loop.

(d)ATP complex called apoptosome. Apoptosome then serves as a caspase-9 activating complex (Adams and Cory, 2002).

Proteolysis is an irreversible process, thus to prevent accidental triggering of cell death, caspase activation is tightly controlled by 'inhibitor of apoptosis proteins' (IAPs) (Ghavami et al., 2008; Gottfried et al., 2004). While some IAPs can only inhibit active caspases, others like, i.e. XIAP can also interfere with caspase-activation process. IAPs are in turn inhibited by Smac/DIABLO released from the mitochondria (Fuchs and Steller, 2011). Caspase-independent apoptosis can be triggered by Apoptosis-inducing factor (AIF), which is a mitochondrial flavoprotein oxidoreductase. This protein is released from mitochondria following apoptotic signals and translocates to the nucleus, where, it induces chromatin condensation (Cande et al., 2002).

8. Importance of apoptosis in central- and peripheral nerve system

Programmed cell death is crucial for normal neural development (Miura, 2011). It regulates the number and types of cells in the developing brain and spinal cord, and plays the key role in constructing an efficient neuronal network. Under pathologic conditions, it is also co-responsible for the loss of neurons associated with neurodegenerative diseases, as well as for physiologic aging (Tendi et al., 2010). The principal molecular components of the apoptosis program in neurons include proteins of the Bcl-2 family, caspases and Apaf1 (Deckwerth et al., 1996; Hakem et al., 1998; Kuida et al., 1996; Motoyama et al., 1995; Yakovlev et al., 2001). Proapoptotic BH3-only Bcl2-family proteins respond to various cell death signals such as DNA damage, oxidative stress, or limited trophic support, by sequestering their antiapoptotic counterparts, thus releasing Bax and Bak from complexes with antiapoptotic Bcl-2 molecules. In turn, Bax and Bak insert itself into outer mitochondrial membrane contributing to cytochrome c release. The insertion of Bax and Bak into the outer mitochondrial membrane largely determines whether the caspase proteolytic cascade will be unleashed.

Although the data on apoptosis in mammalian neurons mainly relies on *in vitro* studies, analysis of animals under experimental conditions and mouse genetic studies have substantially increased our understanding of neuronal cell death regulation. Mice lacking Apaf1 died before birth with enlarged brains due to impaired apoptosis during neuronal development (Ceconi et al., 1998; Yoshida et al., 1998). However, Apaf1 is not required for apoptosis of postmitotic neurons (Honarpour et al., 2000). Motoyama and colleagues demonstrated that disruption of the antiapoptotic *bcl-xL* gene is lethal at day 13 of gestation (Motoyama et al., 1995). Further investigation on *Bcl-xL*-deficient embryos revealed extensive apoptotic cell death in postmitotic immature neurons of the developing spinal cord, brainstem, and dorsal root ganglia and in the hematopoietic system (Los et al., 2002). On the other hand, deletion of pro-apoptotic gene *bax* in mice largely eliminated neuronal cell death within the CNS during development (Hellwig et al., 2011; White et al., 1998). Furthermore, postnatal Bax deficiency leads to prolong cerebellar neurogenesis and accelerates medulloblastoma formation (Garcia et al., 2012). Interestingly, concomitant *bax* deficiency protects *bcl-xL*-deficient embryos from excess neuronal apoptosis, although it did not rescue the embryonic lethality associated with *bcl-xL* deficiency (Shindler et al., 1997). More recently, Ghosh and colleagues (Ghosh et al., 2011) showed reduced apoptotic cell death in the developing nervous system of pro-apoptotic Harakiri (Hrk) deficient mice, while Hrk deficiency did not significantly attenuate the massive apoptosis seen in the *Bcl-xL*-deficient embryos' nervous system. These observations suggest the possible role for other BH3-only molecules, alone or in combination, in regulation of Bax activation in developing neurons.

The role of caspases in neural development has been examined by several groups. Johnson and colleagues demonstrated that DNA damage increased caspase activity in both cultured embryonic telencephalic and postnatal cortical neurons in a p53-dependent manner (Johnson et al., 1999). Since in some cases, p53-mediated neuronal cell death may also occur via caspases-independent pathways, they conclude that the relative importance of caspase activation in neurons depends on the developmental status of the cell and the specific nature of the death stimulus (Holler et al., 2000). Role of the caspases in neural development has been studied using animal models. Gene deletion of both *caspase-3* (Cho et al., 2009) and *caspase-9* (Mughal et al., 2012) in mice resulted in defects within the CNS that include neuronal hyperplasia of the cortex, cerebellum, striatum, hippocampus, and retina, and neuronal disorganization.

9. Alzheimer's disease

AD first described almost 100 years ago by Alois Alzheimer, as a progressive, degenerative disorder of the brain. In industrialized countries approximately 7% of people older than 65 years and about 40% of people older than 80 years are affected (Glass et al., 2010). The estimated risk for developing AD is about 20% for women and 10% for men for age above 65 (Seshadri and Wolf, 2007). The pathology of AD is characterized by an accumulation of misfolded proteins, inflammatory changes and oxidative damage. This result in region-specific loss of synaptic contacts and neuronal cell death (Querfurth and LaFerla, 2010).

Nowadays, around 25–30 million people worldwide are diagnosed with AD and estimations predict a threefold increase by the year 2040 (Minati et al., 2009). AD may have both sporadic and familial etiology. The sporadic form accounts for about 95% of the cases and have a late onset at about age 65, while early onset in some cases in the familial form have been reported (Martin, 2010; Minati et al., 2009). In the familial form, mutations in the genes encoding amyloid precursor protein (APP), presenilin-1 (PSEN1) and presenilin-2 (PSEN2) are associated with AD (Minati et al., 2009). APP is a transmembrane protein that affects β -catenin, anchoring the protein to the actin cytoskeleton and plays an important role in cell-cell adhesion as well as in Wnt signaling (Chen and Bodles, 2007; Nizzari et al., 2007). Upon cleavage of APP through γ -secretase-mediated processes by PSEN1 and PSEN2, the neurotoxic peptide amyloid- β (A β) is formed (Nizzari et al., 2007; Sotthibundhu et al., 2008; Vila and Przedborski, 2003). Abnormal levels of extracellular A β -peptides are found as plaques in patients diagnosed with AD as well as abnormal levels of intracellular neurofibrillary tangles of aggregated proteins containing hyperphosphorylated tau (Martin, 2010). In sporadic cases of AD, apolipoprotein E (ApoE) may modify the γ -secretase activity, although the definitive pathway is yet to be determined. Furthermore, indications of variations in the genes encoding insulin-degrading enzyme (IDE) and ubiquitin-1 (UBQLN1), involved in A β degradation and intracellular trafficking of APP respectively, have been reported (Minati et al., 2009).

Epigenetic mechanisms may also play a role in AD pathogenesis (Day and Sweatt, 2011). Studies on human postmortem brain samples and peripheral leukocytes, as well as transgenic animal models, have identified many links between aging, AD and epigenetic deregulations (Chouliaras et al., 2011), including abnormal DNA methylation and histone modifications (Day and Sweatt, 2011). Though it is still unclear whether these deregulations represent a cause or a consequence of the disease. Twin studies support the notion that epigenetic mechanisms modulate AD risk (Chouliaras et al., 2011). In fact, pharmacological inhibition of DNA methylation in the hippocampus after a learning task infringes memory consolidation in mice (Day and Sweatt, 2011).

More interesting, the promotion of histone acetylation improves learning and memory in a mouse model of AD and increases learning-related gene expression in aged wild-type mice (Kim et al., 2007) suggesting epigenetic regulation of learning and memory in health and disease (Huang and Mucke, 2012).

Various environmental exposures can alter an individual's risk of developing AD, such as nutrition, exposure to a Mediterranean diet, fish and high omega-3 diets, cigarette smoking, head trauma, infections, systemic inflammation, and metal and pesticide exposure (Chouliaras et al., 2011). In addition, psychosocial factors such as education, social network, leisure activities and physical activity, chronic stress, and depression may modify the risk of AD (Ganguli and Kukull, 2010; Qiu et al., 2007). On the other hand, somatic factors related to environmental exposures, such as blood pressure, obesity, diabetes mellitus, cardio- and cerebrovascular diseases, and hyperlipidemia, are also implicated in AD etiology (Ganguli and Kukull, 2010; Qiu et al., 2007). Recent studies have reported a strong correlation between type 2 diabetes and AD (Granic et al., 2009), as type 2 diabetes with hyperinsulinemia increases the risk of AD in elderly people.

10. Parkinson's disease

PD initially described in 1817 by James Parkinson in his "Essay on the Shaking Palsy", whereas the term "Parkinson's disease" was actually coined by J. M. Charcot, over 60 years later. PD is a

progressive neurological incurable disorder with no preventative nor effective long-term treatment strategies (Habibi et al., 2011). It is the second most common neurodegenerative disease after AD. Currently, about 2% of the population over the age of 60, and 0.3% of the general population is affected (Martin, 2010; Samii et al., 2004). The patients suffering from PD display symptoms of motoric instabilities with resting tremor at a typical frequency of 3–5 Hz as the first symptom in 70% of the cases. Other clinical motoric symptoms are rigidity, bradykinesia and postural instability. Non-motoric symptoms include cognitive impairment, depression and sleep disorders (Jankovic, 2008).

The etiology of PD remains uncertain even though it is one of the most common progressive movement disorder in the elderly (Huang and Halliday, 2012). Genetic, environmental risk factors and their interaction play a major role in PD (Fig. 4). Recently, several genes that are directly related to some cases of Parkinson's disease have been discovered. In 1997 a missense mutation in the alpha-synuclein (α -syn) gene was found to be associated with the disease in some families with autosomal dominant mode of inheritance of parkinsonism (Polymeropoulos et al., 1997).

Although 90% of PD cases are sporadic, the study of genetic defects has provided great progress in the understanding of PD molecular mechanisms (Ali et al., 2011). Mutations in the leucine-rich repeat kinase 2 (LRRK2, PARK8) are the most frequent known cause of familial autosomal dominant PD (Zimprich et al., 2004). More recently a common genetic variant (LRRK2 G2385R) have

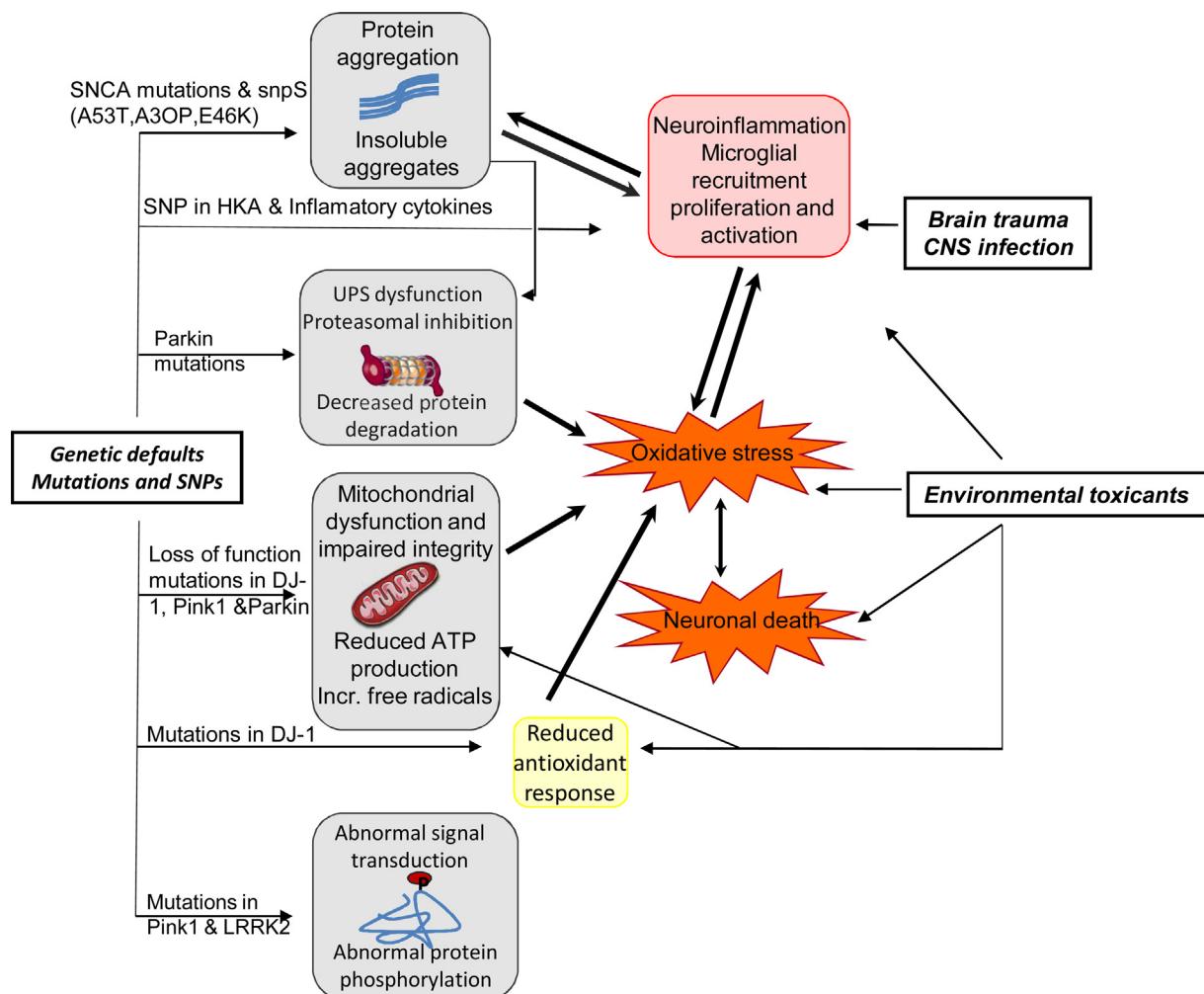


Fig. 4. Role of genetic factors and their interplay with environmental factors in PD. In dopaminergic neurons oxidative stress can occur due to defects of genes known to play a role in the etiology of PD, such as PINK1, LRRK2. Oxidative stress and other cellular-stress stimuli may lead to neuronal cell death by disrupting the function of PD related gene products such as Parkin, DJ-1 or PINK 1. This may lead to the interference with the function of mitochondria or induction of inflammatory processes within neuronal tissues.

been identified to increase the risk of PD in Taiwanese Chinese. *LRRK2* Gly2385Arg another variant have also been identified in 2006. The presence of genetic defects in the sporadic cases of PD as well as the high variable onset age and phenotypic variation in the inherited PD form emphasizes the crucial role of genetic defects in the development of PD (Ali et al., 2011).

Although the clear involvement of environment in PD remains debated, many risk factors have been identified and are directly or indirectly related to the disease. In the 1980s, it was found that exposure to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), caused PD-like symptoms. Paraquat and rotenone, in addition to other environmental toxins, and other factors that cause mitochondrial dysfunction have been reported as high risk factors for PD (Habibi et al., 2011). Various studies suggest that PD neurodegeneration is the result of a gene environment complex affecting various stages of progressive mechanisms leading to the neuronal death in PD (see Fig. 4) (Ali et al., 2011).

11. Huntington's disease

HD is a neurodegenerative disorder affecting parts of the brain, which regulates the movements, mainly the basal ganglia, causing the characteristics of uncontrolled movements called chorea (Walker, 2007). Other symptoms of HD are dystonia, incoordination, cognitive impairment and behavioral difficulties. The prevalence peak in white populations amounts to about 5–7 cases per 100 000, except from some rural areas of inbreed with higher frequency. HD is an autosomal dominant disorder, caused by a mutation in the Huntington gene located on chromosome 4, with a typical onset at age 35–44. The gene contains a multiple repeat of CAG nucleotides encoding glutamine. More than 35 repeats are associated with the disease and the age of onset is lower with increasing number of repeats. The role of Huntington protein (htt) is currently unclear. Huntington may have anti-apoptotic properties of the protein as well as the control of brain-derived neurotrophic factor production, vesicular transport, neuronal gene transcription and synaptic transmission (Cattaneo et al., 2005). The mechanism of the neurodegenerative process in HD is not fully defined. However, one explanation involves the cleavage of the mutated protein. Created n such way fragments with high poly-glutamine (pQ) content may form aggregates through hydrogen bonds, and mechanically stop transmission of neurotransmitters between neurons (Rubinstei and Carmichael, 2004). Another explanation of the cytotoxicity is the binding between mutated htt aggregates with the small guanine nucleotide-binding protein Rhes, located in the striatum, and inducing sumoylation of the aggregates (Subramaniam et al., 2009). Furthermore, suggestions of pathogenic mechanisms include excitotoxicity (the process of neuronal damage by neurotransmitter, through overstimulation of receptors), mitochondrial dysfunction, increased activity of caspases, autophagy, proteolytic cleavage by proteasomes and aspartyl proteases, and abnormal histone modifications (Sadri-Vakili and Cha, 2006). The available treatment includes, i.e. amantadine, remacemide, levetiracetam and tetrabenazine. The pharmacologic intervention is able to reduce the symptoms of HD, but there are currently no drugs to stop or reverse the progress of the disease (Walker, 2007).

12. Amyotrophic lateral sclerosis

ALS is caused by the degeneration of motor neurons in the central nervous system and is characterized by muscle weakness and atrophy, spasticity, paralysis and in some cases dementia (Martin, 2011). With a typical onset between 35 and 50 and a life expectancy after diagnosis of 3–5 years, the disease is affecting about 2 per 100 000 each year (Blackhall, 2012). The majority,

about 90–95% of the patients has no family history of ALS and the cause of this sporadic form is unclear. In the familial form, mutations in the superoxide dismutase 1 (SOD1) gene are the most common cause of ALS (Carri and Cozzolino, 2011). SOD1 is an antioxidant enzyme protecting neurons from free superoxide radicals and can, in the mutated form, stimulate protein aggregation that might lead to apoptosis. Mutant forms of the protein TDP-43 encoded by the *TARDBP* gene (Sreedharan et al., 2008), as well as mutations in the *FUS* gene encoding an RNA binding protein (Vance et al., 2009), are also among the genes associated with familial ALS (Martin, 2011). The mechanism of the pathology is unclear; however, suggestions include mitochondrial pathobiology (Martin, 2011), lactate dyscrasia (Vadakkadath Meethal and Atwood, 2012), immune system alterations (Mantovani et al., 2009) and protein aggregation (Shaw, 2005). Currently, riluzole is the only therapy available on the market, however, the median prolonged life expectancy is only 2–3 months (Miller et al., 2012).

13. Neuroinflammation in neurodegenerative diseases

Inflammation is a self-defensive reaction against various pathogenic stimuli that helps the organism respond to pathogens or irritation. Nevertheless, inflammation when chronically impaired may become a harmful self-damaging process that can cause serious damage to host's own tissue. While the CNS has been known as an immune privileged organ, increasing evidence support the involvement of chronic inflammation in various neurodegenerative disorders including AD, PD and ALS (Banati et al., 1998; McGeer et al., 1988; Raine, 1994). In this context, chronic inflammation-mediated tissue damage can be particularly harmful to the brain, since neurons are generally irreplaceable.

13.1. General dynamics of neuroinflammation in neurodegenerative diseases

Neuroinflammation is a term describing cellular and molecular processes, which encompasses activation of microglia and astrocytes and infiltration of peripheral immune cells. In the central nervous system, microglia, antigen presenting brain immune cells (or macrophages), are the innate immune components of the CNS. Under normal condition, they play major role in the inflammatory process and insure the CNS parenchymal integrity. Activated microglia at the site of inflammation change their morphology, express increased levels of MHC antigens and become phagocytic (Hayes et al., 1987). They release inflammatory cytokines that amplify the inflammatory response by activating and recruiting other cells to the brain lesion. On the other hand, uncontrolled activation of microglia may directly be toxic to neurons. The toxicity has been observed in numerous neurodegenerative disorders, and it is mediated by releasing various toxic substances including inflammatory cytokines (IL-1 β , TNF- α , IL-6), NO, PGE, and superoxide. In addition, activated microglia has the ability to phagocytose not only damaged cell debris but also neighboring intact cells, thus causing neurodegeneration. Though microglia can have both a protective and a devastating role, its activation and functions in NDD plays a more significant role in mediating the diseases than in protecting neurons, among them AD, PD, ALS (Banati et al., 1998; Dickson, 1997; Raine, 1994).

13.2. Alzheimer's diseases and neuroinflammation

The suggestion that inflammation may participate in AD first came up more than two decades ago. Many investigators have concluded that neuroinflammation contributes to neuronal damage in the brain during AD (Akiyama et al., 2000). In fact,

microglia are found in a hyper-activated state in close anatomical proximity to senile plaques within the AD brain. In this activated state, microglia produces various pro-inflammatory cytokines and other immune mediators that create a neurotoxic environment (proteolytic enzymes, excitatory amino acids, quinolinic acid, complement proteins, reactive oxygen intermediates, and nitric oxide (Cassarino et al., 1997; Chao et al., 1992; Gao et al., 2002; McGuire et al., 2001) leading to disease progression (Akiyama et al., 2000; Wyss-Coray, 2006). For instance, the ratio of the pro-inflammatory cytokine IL-1 to the anti-inflammatory cytokine IL-10 is greatly elevated in the serum of AD patients, resulting in a chronic neuroinflammation. In addition, the accumulating loss of neurons that characterizes AD further contributes to generation of debris and keeps microglia in an indefinitely activated state that further amplifies its neuro-toxic production. A β itself may act as a pro-inflammatory agent causing the activation of many of the inflammatory components. The involvement of neuroinflammation in AD has further been supported by the findings that patients who took non-steroidal anti-inflammatory drugs had a lower risk of AD than those who did not.

13.3. Parkinson's disease and neuroinflammation

PD is also recognized to have an inflammatory component (Qin et al., 2007). As seen in AD, the brain of PD patient is also characterized by an upregulation of HLA-DR antigens and the presence of HLA-DR-immunopositive and highly reactive microglia (McGeer et al., 1988). Activated microglia-mediated dopaminergic neuronal degeneration has been demonstrated using animal models (Gao et al., 2002) showing that microglia plays a central role in rotenone-induced dopaminergic neuronal degeneration. Moreover other studies demonstrated that the inhibition of microglial activation prevents dopaminergic neuronal loss in MPTP-treated mice (Wu et al., 2002). In addition, non-steroidal anti-inflammatory drugs reduce PD (Wahner et al., 2007) confirming the involvement of innate immunity in PD. Adaptive immunity is also involved in PD (Huang and Halliday, 2012). In PD brain the BBB (blood brain barrier) is disrupted due to activated microglia and monocytes (Stone et al., 2009) and IgG, has been shown bound to dopamine neurons in the substantia nigra of idiopathic and familial PD patients, but not in age-matched controls (Orr et al., 2005).

13.4. Amyotrophic lateral sclerosis and neuroinflammation

Inflammation in ALS is characterized by gliosis and the accumulation of large numbers of activated microglia and astrocytes. Activation of glia in ALS is associated with an elevated production of cytotoxic molecules such as ROS, inflammatory mediators such as COX-2, and proinflammatory cytokines such as IL-1 β , TNF- α , and IL-6 (McGeer and McGeer, 2002). In addition, major histocompatibility complex molecules and complement receptors are highly expressed by reactive microglia in the primary motor cortex and in the anterior horn of the spinal cords of ALS patients (McGeer and McGeer, 2002).

Studies supporting a detrimental role for activated glial cells in ALS include the finding that the chronic administration of lipopolysaccharide or the deletion of the receptor for the chemokine, fractalkine, is associated with a robust astrogliosis and microgliosis and an exacerbated ALS-like phenotype in mutant SOD1 Tg mice (Cardona et al., 2006). Moreover, once activated, astrocytes become capable of killing previously healthy neighboring MNs (Cassina et al., 2002). After activation, glial cells start producing a host of toxic molecules (Kreutzberg, 1996) which in turn mediate the glial harmful action on neighboring neurons.

14. Autophagy hyperactivation or failure associated with neuronal cell death

In neurodegenerative disorders impairment at distinct steps of autophagy including autophagosome formation, cargo recognition, transport, autophagosome/lysosome fusion, autophagosome clearance and cargo degradation, conducts to the buildup of damaged organelles altered or pathogenic protein, while defeating autophagy's crucial prosurvival and antiapoptotic effects on neurons (Fig. 5). The differences in the location of defects within the autophagy pathway and their molecular basis influence the pattern and pace of neuronal cell death in the various neurological disorders.

Although proposed to be a primary or irreversible death trigger, autophagy is now widely considered as both a vital homeostatic mechanism in healthy neuronal cells as described in previous paragraphs as well as a cytoprotective response when further induced in chronic neurodegenerative disorders (Marino et al., 2011; Moreau et al., 2010; Nixon and Yang, 2012). This protective effect is not simply a function of autophagy liberating fuels for cells, but appears to be related to decrease in the amount of mitochondria (because of mitophagy). This, in turn, results in less release of toxic molecules like cytochrome c from mitochondria in response to proapoptotic insults. Koike and colleagues reported in vivo evidence of neuronal cell death requiring autophagy in the mammalian brain.

Although autophagy is mostly neuroprotective, can it also be deleterious? Although expression autophagic cell death (ACD) suggests that cell death is executed by autophagy, recent data from the Kroemer laboratory (Shen et al., 2011) using high-throughput chemical screens failed to demonstrate that any of these compounds killed cells via autophagy. The results of such studies could be influenced by a possible role of ATG genes in other functions involved in cell death unrelated to autophagy. And some scientist argue that rapidly dividing mammalian cells as cancer cells are not the most likely situation for finding pure ACD (Clarke and Puyal, 2012). However, ACD can be now defined on the basis of the following set of criteria: (i) ACD must be a distinct death mechanism, independent of apoptosis or necrosis. Thus, situations in which autophagy triggers apoptosis or necrosis, or occurs in parallel with them, are excluded even when the autophagy has been clearly shown to promote cell death (ii) there is an increase in autophagic flux, and not just an increase in the autophagic markers, in the dying cells; (iii) suppression of autophagy via either pharmacological inhibitors or genetic approaches is able to rescue or prevent cell death. (iv) autophagy must "...be itself responsible for the final dismantling of cellular content and hence execute a lethal pathway" (Shen et al., 2012). Debate continues as to whether a definition of ACD should include this last criterion (Clarke and Puyal, 2012). In light of this new definition, in mammalian cells, however, ACD is uncommon. It is not entirely clear that autophagy is sufficient to execute death without help from apoptosis or necrosis (Nixon and Yang, 2012). In some cases, autophagic vacuole proliferation occurs in the context of cell death executed by caspases and may facilitate execution but is not essential for death.

Autophagy inhibition by 3-methyl adenine (3MA) has been used to implicate autophagy in cell death execution by showing blocked or delayed cell death after this treatment. Although the interpretation of protection via autophagy inhibition should be qualified because this inhibitor has a dual role in modulation of autophagy via different temporal patterns of inhibition on class I and class III phosphoinositide 3-kinase (Wu et al., 2010). Also, in most of these cases, cytoprotection is not absolute and death finally results via cytochrome c release and caspase cascade activation indicating that an apoptotic pathway may be operating

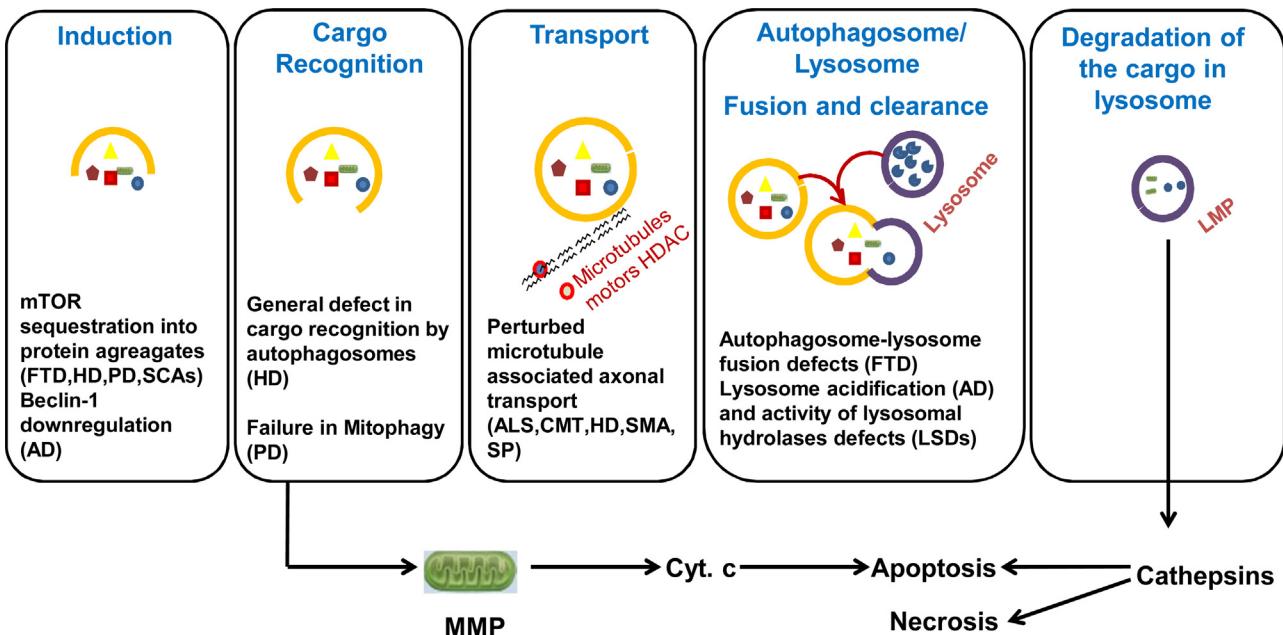


Fig. 5. Distinct steps of the autophagic pathway can be altered in a variety of neurodegenerative disorders and possible links to neuronal cell death. The different alterations linked to neurodegeneration affecting autophagic flux including reduced autophagy induction or enhanced autophagy repression; altered cargo recognition; inefficient autophagosome/lysosome fusion; inefficient autophagosome clearance; and inefficient degradation of the autophagic cargo in lysosomes. Examples of neurodegenerative diseases for which alteration in each step are shown. The autophagy alteration may promote neuronal cell death via two possible mechanisms: (1) impairment of cargo degradation in lysosome leading to lysosomal membrane permeabilization (LMP) and cathepsin release into cytosol, thereby inducing either apoptotic or necrotic cell death; (2) failure in mitophagy resulting in accumulation of damaged mitochondria and mitochondrial membrane permeability (MMP) leading to cytochrome c release and apoptotic cell death AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; CMT, Charcot-Marie-Tooth disease; FTD, fronto-temporal dementia; HD, Huntington's disease; LSDs, lysosomal storage disorders; PD, Parkinson's disease; SCAs, spino-cerebellar ataxias; SMA, spinal muscular atrophy; SP, spastic paraplegia.

in parallel (Canu et al., 2005; Kaasik et al., 2005; Uchiyama, 2001). Furthermore, cathepsin inhibition also blocks or delays cell death in many models, further supporting the idea that lysosomal destabilization and cathepsin release finally triggers apoptosis (Canu et al., 2005; Kaasik et al., 2005; Uchiyama, 2001).

Autophagy induction is frequently associated by up-regulated hydrolase synthesis and increased lysosome biogenesis (Settembre et al., 2011). Under circumstances in which lysosomes are destabilized or their function is compromised, it is more likely that autophagy inhibitors attenuate autophagic stress on compromised lysosomes by decreasing delivery of autophagic cargo rather than by attenuating an overaggressive auto cannibalistic process. Indeed, healthy neurons in culture seem to tolerate robust autophagy induction (Lee et al., 2011) except when lysosomal function is also impaired. In situation which prevent of autophagy is neuroprotective, counteraction of lysosome destabilization could be more suitable to the mechanism of cytoprotection than is the blockade of authentic ACD.

As described above, there has been skepticism that mammalian cells can die through excessive autophagy, however recently Lamy et al. provide support for the idea that deregulated autophagy could result in cellular auto destruction in multiple myeloma. These cells utilize caspase 10 to restrain autophagy and undergoes ACD upon its inhibition or removal (Lamy et al., 2013). In contrast to autophagy hyperactivation, autophagy failure is commonly linked to a lysosome dependent form of cell death (Boya and Kroemer, 2008) which is relevant to the loss of neurons in various neurodegenerative diseases. Loss of function of lysosomal enzymes or structural proteins leads to defects at autolysosomal stages of autophagy. A neuronal cell death involving autophagy is seen in lysosomal storage disorders owing to these defects, although the evidence is mostly *in vitro*.

Depletion of factors critical for autophagy induction or autophagosome formation such as Atg5, Atg7 or FIP200, induces

neuronal cell death and cytoplasmic accumulation of organelles or ubiquitinated proteins (Komatsu et al., 2006; Liang et al., 2010). In neurodegenerative disorders impairment at distinct steps of autophagy, can trigger neuronal cell death in several ways (Fig. 5). When, autophagosome clearance and cargo degradation steps are compromised, autolysosomes/lysosomes accumulate mutant and oxidized proteins, protein oligomers and aggregates, damaged organelles, and other incompletely digested products. Such conditions increase the permeability of lysosomal membranes causing hydrolases release into the cytoplasm (Kroemer and Jaattela, 2005). Both exogenous (Erdal et al., 2005) and endogenous factors are able to disrupt lysosomal membrane integrity directly and induce rapid lysosome-dependent cell death (Boya and Kroemer, 2008; Johansson et al., 2010; Repnik et al., 2012). Endogenous factors able to induce lysosomal membrane permeabilization (LMP) includes a few proteins/peptides implicated in AD, such as Ab and ApoE, calpains, ceramide, certain caspases, oxidized lipids or lipoproteins, reactive oxygen species (ROS), and sphingosine. Factors that cause disruption of lysosomal membranes are likely to induce necrosis during which released lysosomal hydrolases participate as both a trigger and as executioners along with caspases that are activated by cathepsin-mediated cleavage (Hartmann et al., 2000; Werneburg et al., 2004). Slower lysosomal cathepsins release may first activate apoptotic cascades via cytochrome c release from mitochondria, degradation of antiapoptotic Bcl-2 family, and activation of Bax that releases mitochondrial AIF and can also induce LMP. In a pathological situation in which distinct steps of autophagy are impaired, the resultant increase in numbers of damaged mitochondria can trigger apoptosis through the intrinsic pathway and via ROS generation that oxidizes membrane lipids and destabilizes the lysosome membrane. Reduced autophagic elimination of other proapoptotic factors, such as activated caspases, may also accelerate apoptosis under these conditions (Yang et al., 2008).

15. Autophagy and neurodegenerative disease

Below, we discuss various neurodegenerative disorders including Alzheimer's, Parkinson's, Huntington's, and amyotrophic lateral sclerosis that are associated with impairment in the different stages of autophagy (Fig. 5).

15.1. Alzheimer's diseases – disturbed autophagy as a contributing factor

One hypothesis on the etiology of AD is based on the accumulation of damaged mitochondria in the neurons. Accordingly, translocation of misfolded proteins into the mitochondrial membrane leads to the disruption of oxidative phosphorylation (Rhein et al., 2009) and subsequent autophagy activation (Smaili et al., 2011). Lysosomes are essential components of autophagy while autophagic degradation of damaged mitochondria is an important factor in quality control of mitochondria (Gusdon et al., 2012). Thus, a decline in autophagy efficiency during aging (Rubinsztein et al., 2011; Taylor and Dillin, 2011) leads to accumulation of A β and α -syn oligomers in the mitochondrial membrane and the release of cytochrome c. This event can trigger the caspase cascade that results in extreme cell death and neurodegeneration (Hashimoto et al., 2003). In line with this notion is the observation that Zinc ion (Zn^{2+}) supplementation improved mitochondrial function and ameliorated hippocampal A β and tau pathogenic signs in a mouse model of AD. Notably, dietary Zn^{2+} supplementation reduced intraneuronal A β , tau pathology, and prevents mitochondrial deficits. Zinc chelation, on the other hand appears to have toxic effect, at least in some cell types (Hashemi et al., 2007). This treatment also restored BDNF levels and prevented hippocampal-dependent cognitive deficits. Furthermore, detection of massive neuronal accumulation of autophagosomes in dystrophic and degenerating neurites, pointed

to deficit in axonal transport as a possible pathologic reason for AD (Silva et al., 2011).

Mobile mitochondria can halt in regions with high metabolic demands (Sheng and Cai, 2012), thus aberrant axonal transport could influence effective function of mitochondria. On the other hand, an in vitro study has reported an association between inhibition of lysosomal proteolysis and disturbed axonal transport in cortical neurons. The observed neuritic dystrophy was reversed by enhancing lysosomal proteolysis (Lee et al., 2011). This connection maybe exerted via microtubule-associated protein 1S (MAP1S). MAP1S interacts with LC3 (autophagosome-associated light chain 3), LRPPRC (mitochondrion-associated leucine-rich PPR-motif containing protein) as well as microtubules, and thereby may affect integration of components of autophagosomes (Xie et al., 2011). We have briefly summarized the role of macroautophagy in AD in Table 1.

15.2. Parkinson's disease – autophagy as possible protective factor

Accumulation of α -syn-containing Lewy bodies in substantia nigra neurons is the hallmark of PD (Mizuno et al., 2008). Recently scientists have focused more on the production, function and degradation of α -syn oligomers (Sulzer, 2010; Vekrellis et al., 2011). Wild-type α -syn is degraded by both UPS and macroautophagy, especially via CMA (Cuervo et al., 2004), while its mutant form gain a toxic function and binds to and blocks CMA receptors (Cuervo et al., 2004). Reduced CMA function then causes accumulation of more aggregated proteins and worsening of the situation (Alvarez-Erviti et al., 2010; Cuervo et al., 2004). Although mutant α -syn is partly degraded through macroautophagy, it also aggregates and produces oligomers, as overexpressed wild type α -syn and dopamine modified α -syn do (Sulzer, 2010). α -Syn oligomers seem to interact with organelle lipid membranes (Sulzer, 2010) and interfere with their normal function leading

Table 1
Macroautophagy in proteopathic neurodegenerative diseases and their therapeutic modulators.

Proteopathic neurodegenerative disorders	Macroautophagy	Chaperon-mediated autophagy	Potential therapeutic modulators
Alzheimer's disease	Macroautophagy is transcriptionally up-regulated (Lipinski et al., 2010) Autophagosome maturation is impaired (Yu et al., 2005) Macroautophagy is inhibited by mutated presenilin-1 in a familial form of AD (Cataldo et al., 2004)	CMA degrades regulator of calcineurin-1 (RCAN1) (Liu et al., 2009) CMA degrades Tau proteins (Wang, 2009)	Rapamycin (Mendelsohn and Lerrick, 2011; Spilman et al., 2010) Resveratrol (Kim et al., 2007; Vingtdeux et al., 2011) Nicotinamide (Liu et al., 2013a) Latrepirdine (Steele and Gandy, 2013)
Parkinson's disease	Macroautophagy degrades wild-type and mutated α -syn (Vogiatzi et al., 2008)	CMA degrades wild-type α -syn (Cuervo et al., 2004; Vogiatzi et al., 2008) CMA is inhibited by mutated α -syn (Cuervo et al., 2004) CMA activity is reduced in the brain of PD patient (Alvarez-Erviti et al., 2010)	Rapamycin (Dehay et al., 2010; Mendelsohn and Lerrick, 2011) Trehalose (Sarkar et al., 2007) Kaempferol (Filomeni et al., 2012) Resveratrol (Wu et al., 2011) Isorhynchophylline (Lu et al., 2012)
Huntington's disease	Macroautophagy is debilitated to cargo recognition (Martinez-Vicente et al., 2010) Macroautophagy degrades Htt43Q (Carra et al., 2008) Macroautophagy is impaired in early stages of HD (Koga et al., 2011)	CMA degrades mutated Htt (Bauer et al., 2010) CMA is up regulated in early stage of HD (Koga et al., 2011)	Trehalose (Sarkar et al., 2007) Rapamycin (Mendelsohn and Lerrick, 2011; Ravikumar et al., 2002) Rilmenidine (Rose et al., 2010)
Amyotrophic lateral sclerosis	Macroautophagy degrades mutated and wild type SOD1 (Hetz et al., 2009; Kabuta et al., 2006) Macroautophagy degrades TDP-43 (Johnson et al., 2010) Macroautophagy is induced by mutated SOD1 (Crippa et al., 2010b; Li et al., 2008)	No available data	Lithium (Fornai et al., 2008) Resveratrol (Kim et al., 2007) Trehalose (Gomes et al., 2010)

to mitochondrial damage and fragmentation (Sulzer, 2010; Vekrellis et al., 2011) as well as lysosomal and proteosomal dysfunction (Sulzer, 2010).

A number of studies have suggested the attenuation of macroautophagy and UPS function (Dehay et al., 2010) or aberrant and incomplete progress in degradation pathways (Cuervo et al., 2004) as important initiators of PD (Dehay et al., 2010). Besides, numerous in vitro studies have demonstrated that induction of autophagy with different types of compounds such as trehalose (Dehay et al., 2010; Mendelsohn and Lerrick, 2011), kaempferol (Filomeni et al., 2012), Isorhynchophylline (Lu et al., 2012) and resveratrol (Wu et al., 2011), results in improvements in the molecular traits of PD.

The other concept of PD etiology returns to the mitochondrial dysfunction mediated by protein products of the mutant genes that are recognized in the hereditary PD. PINK1-parkin pathway is suggested as a mitochondrial morphology controller. It regulates mitochondrial function and its aberrant activity could induce mitophagy (Lazarou et al., 2012; Narendra et al., 2008). Another function attributed to PINK1 is its interaction with beclin-1 that results in the elevation of basal and starvation-induced autophagy. Furthermore, mutations in DJ-1 that cause loss of function of this gene lead to mitochondrial dysfunction, elevated levels of ROS and decreased lysosomal-autophagic degradation (Krebiehl et al., 2010). These events result in the accumulation of damaged mitochondria (Krebiehl et al., 2010). Aberrant accumulation of autophagosomes in PD, that used to be interpreted as an abnormal induction of autophagy is alternatively suggested to be due to defective autophagic clearance. This defect has been hypothesized as a consequence of alterations in the microtubule network driven by mitochondrial dysfunction (Arduino et al., 2013). Thus, specific defects in selective autophagy or cargo recognition may be sufficient to cause PD (Narendra et al., 2008). Taken all data together, activation of autophagy seems to be a good strategy to fight progression in PD. Table 1 briefly summarized the role of macroautophagy in PD.

15.3. Huntington's disease – potential pro-survival effect of autophagy

Neuronal intranuclear inclusions were initially offered as the molecular pathogenic cause of HD (Davies et al., 1998). Further cellular studies however showed that these inclusion bodies could ameliorate survival of the rat embryonic striatal neurons (Arrasate et al., 2004). Now it has been revealed that mutant Htt when inside the inclusion bodies, and as aggregated forms are less toxic than the soluble form of the protein (Zuccato et al., 2010).

Another hypothesis on the cause of HD suggests that mitochondrial defects may play a central role (Pickrell et al., 2011). Investigations on the immortalized cell lines from HD patients have shown that the presence of one HD allele results in the mitochondrial membrane hyperpolarization and increased susceptibility to apoptosis. Addition of another HD allele to these cells increased the number of cells that contained autophagic vacuoles with more cannibalistic activity (Mormone et al., 2006). These findings along with results of other studies (Ravikumar et al., 2006), suggest that mitophagy eliminates damaged mitochondria and thus prevents the release of cytochrome c and other proapoptotic proteins, leading to the inhibition of cell death and neurodegeneration.

Recent findings have led to the hypothesis that autophagic vacuoles form normally and even with more velocity in cells from both HD patients and mouse models of HD. These vacuoles cannot trap aggregated mutant Htt (Martinez-Vicente et al., 2010). The authors provided evidence that failure of autophagy in HD is a complex process. They have demonstrated that, although

autophagosome formation and degradation are normal in both murine models and HD patients, cargo recognition is severely affected. This leads to the accumulation of undegraded cytoplasmic cargo (including huntingtin-containing aggregates) that constitutes a possible damage source in neuronal cells. On the other hand, results of another study show that elevation in the lysosomal proteases has helped the mutant Htt clearance from the HEK cells via macroautophagy (Liang et al., 2011). In line with this report are data of in vivo and in vitro studies that show the beneficial effects of different types of autophagy inducers in HD (Mendelsohn and Lerrick, 2011; Wang et al., 2011a). The role of macroautophagy in HD is briefly summarized in Table 1.

15.4. Convolved role of autophagy in the etiology and progression of amyotrophic lateral sclerosis

Degeneration of spinal motoneurons leads to respiratory failure and death in ALS. ALS has been considered as a multifactorial disease with endoplasmic reticulum stress, oxidative damage and genetic factors being proposed as some of its pathogenic reasons (Pasinelli and Brown, 2006). It has been established that elevated levels of aggregated proteins can cause UPS dysfunction (Crippa et al., 2010a) and subsequently, compensatory activation of autophagy (Korolchuk et al., 2010). Thus, impairment of UPS (Cheroni et al., 2005) and induction of autophagy have been shown in spinal neurons from animal models of ALS (Li et al., 2008) and in post mortem samples from ALS cases (Sasaki, 2011). Furthermore, an association between the mutant forms of valosin-containing protein (VCP) with an autosomal dominant ALS has been observed (Johnson et al., 2010). VCP, an ATP-driven chaperon is essential for the maturation of autophagosomes that contain ubiquitin and is suggested to have a role in the mitochondrial quality control and autophagy (Yamanaka et al., 2012).

Mitochondrial dysfunction has been offered as a converging point for the multiple pathways that cause apoptosis activation and neuronal loss in ALS (Reyes et al., 2010; Shi et al., 2010). The role of disturbance in the mitochondrial function and transport in the pathogenesis of ALS has been revealed using transgenic SOD1 mice as a familial model of ALS (Magrane et al., 2009). The cause of mitochondrial malfunction may be linked to the accumulation of aggregated misfolded proteins, frequently SOD1 and TAR DNA-binding protein 43 kDa (TDP-43) (Neumann et al., 2006; Shi et al., 2010). These aggregates form in the ubiquitin-containing inclusions in cell bodies and axons of motoneurons (Neumann et al., 2006). Notably, SOD1 is basically a cytosolic protein but it partly deposits in the intermembrane spaces of mitochondria in mutant SOD1 transgenic mice, a fact that can explain its deleterious effect on the mitochondrial function (Magrane et al., 2009).

Induction of autophagy, elimination of damaged mitochondria and aggregated proteins has beneficial effects in slowing the ALS progression (Crippa et al., 2010b; Fornai et al., 2008; Hetz et al., 2009). Although autophagy dysregulation has been proposed as a pathogenic base of ALS (Reviewed in Chen et al., 2012), knocking-out of motor neuron-specific autophagy machinery failed to induce ALS in mice. In the same study, ablation of the UPS in motor neurons reproduced ALS (Tashiro et al., 2012). Additionally, no systemic macroautophagy dysfunction has been detected in lymphomononuclear cells of ALS patients (Sala et al., 2012). Another study showed that daily consumption of lithium delayed ALS progression in affected humans. This neuro-protective effect was accompanied by the activation of autophagy in motor neurons in G93A mouse model of ALS (Fornai et al., 2008). Upregulation of autophagic genes displays similar outcomes in *Caenorhabditis elegans* model of ALS (Li et al., 2013).

Autophagy inducers like trehalose (Gomes et al., 2010) and resveratrol (Kim et al., 2007) have also shown beneficial effects by

decreasing protein aggregation and promoting neuronal survival. However, rapamycin which is a mTOR dependent inducer of autophagy, has had detrimental effects on motor neurons in the SOD1 mouse model of ALS (Zhang et al., 2011). Results of a recent study show that this controversy may be related to the stage of the disease. Accordingly, food restriction, another established autophagy inducer, show potential protective effects on the spinal cord of SOD1-G93A mice, only at onset stage but not at pre-end stage of ALS (Zhang et al., 2013). Table 1 briefly summarizes the role of macroautophagy in ALS.

15.5. Autophagy and neuroinflammation

As we have described before, neuroinflammation is implicated in the progressive nature of several neurodegenerative disorders and is described in almost all lysosomal storage diseases (LSDs) with neurological involvement (Farfel-Becker et al., 2011; Jeyakumar et al., 2003; Ohmi et al., 2003). Autophagy may play an essential function in the control of inflammation and immunity. Gutierrez and colleagues demonstrated that autophagy was involved in the removing microbes such as mycobacterium tuberculosis (Gutierrez et al., 2004a). Yu et al. (2006) showed that autophagy selectively degraded catalase leading to the accumulation of ROS and non-apoptotic death of macrophages. Therefore, therapeutic strategies to inhibit neuroinflammation by the regulation of autophagy might be helpful in seeking effective new target treatments for neurodegenerative diseases.

Both, oxidative stress and neuroinflammation have been involved to advance cognitive destruction in AD as they can facilitate A β generation and NFTs formation (Agostinho et al., 2010; Cai et al., 2013) and finally throw in to the progressive cognitive deficits of AD (Majumder et al., 2011; Rasool et al., 2012). Previous reports have revealed that autophagy inducer rapamycin recovers learning process and memory in the course of the inhibition of A β and tau accumulation by interfering with several signaling cascades (Liu et al., 2013b) that include interactions between oxidative stress and neuroinflammation (Galasko and Montine, 2010; Galimberti and Scarpini, 2011). Therefore, rapamycin is thought to exert its neuroprotective actions via its antioxidant, anti-inflammatory, and autophagy inducing capabilities (Chen et al., 2013; Marobbio et al., 2012).

16. Apoptosis and neurodegenerative disease

16.1. Apoptosis in Alzheimer's diseases

The exact mechanisms of neuronal degeneration in AD are still unknown. Available data presents some abnormalities in the metabolism of amyloid precursor protein (APP) as a causative factor, which can results in mitochondrial dysfunction and eventually cell death. Whenever there is an overexpression of APP, its metabolite, A β peptide, will overload. Toxic effect of A β is manifested by ROS generation, apoptosis induction and impaired memory (Lustbader et al., 2004). Although most deleterious effects of A β is attributed to A β deposits (Abramov et al., 2004; Picone et al., 2009), extracellular A β (i.e. released from dying cells) can enter other cells and cause mitochondrial dysfunction (Anandatheerthavarada et al., 2003; Picone et al., 2009; Resende et al., 2008b). Therefore, APP has been the subject of intense research as one possible cause for mitochondrial dysfunction in AD (Fuchs and Steller, 2011; Hirai et al., 2001).

With this regard, in vivo and in vitro experiments have shown that soluble A β impairs mitochondria metabolism by decreasing cytochrome oxidase activity and increasing hydrogen peroxide generation (Manczak et al., 2006). Moreover, A β can interact with Cyclophilin-D, the mitochondrial modulatory component of

mitochondrial mPTP, and increase synaptic stress with disturbing effects on learning and memory of AD patients (Du et al., 2008). In an animal model, knocking down of Cyclophilin-D encoding gene ameliorated deleterious effects of A β (Ceconni et al., 1998). A recent study conducted on HT22 line of murine hippocampal cells and the APP/PS mouse model of AD have also shown that cytochrome c release from the mitochondria was mediated not only by the exogenous treatment of Ab1–42, but also by the mitochondria-specific accumulation of Ab1–42. The same work also revealed that exogenously treated Ab1–42 enters the intracellular compartment through clathrin-mediated endocytosis, and that mitochondria-specific Ab1–42 accumulation was a sufficient event to induce not only mitochondrial dysfunction, but also neuronal death (Cha et al., 2012).

Death receptors DR4 and DR5 were shown to mediate cerebral microvascular endothelial cell apoptosis that was induced by oligomeric A β peptide (Fossati et al., 2012). A β peptide also induces caspase-3-dependent apoptosis in primary culture of astrocytes. Overexpression of wild-type APP in CHO cells also induced caspase-3 activation and nuclear fragmentation. In this context, caspase-3 activated apoptosis was due to the aggregation of APP in mitochondria. The finding that opening of mPTP was glutathione-sensitive suggests a novel pro-oxidant role for APP (Bartley et al., 2012). Results of another study on the primary rat cortical neuron cultures, suggested AIF-induced death as the mechanism of caspase-independent apoptosis which happens following A β treatment (Yu et al., 2011).

RanBP9 is a scaffold protein that is increased in brains of AD patients (Lakshmana et al., 2010). Levels of RanBP9 also increase by four-fold in brains of FAD mutant APP transgenic mice. The same study also revealed that RanBP9 activates/dephosphorylates cofilin, which is a crucial tuner of mitochondrial induced apoptotic cell death (Klamt et al., 2009) and actin dynamics (Kim et al., 2010). Endoplasmic reticulum (ER) stress has been presented as another causative factor in AD by affecting tau phosphorylation and Ca $^{2+}$ regulation (Resende et al., 2008a,b). The E693 δ mutation in APP in transfected HEK293 and COS-7 cells caused accumulation of A β in ER, subsequent increased ER stress markers, such as Grp78 and phosphorylated eIF2 α , and finally stress-induced apoptosis in the ER (Nishitsui et al., 2009).

16.2. The role of apoptosis in the etiology and progression of Parkinson's disease

Although a spectrum of cell death have been detected in PD (Reviewed in Perier et al., 2012) apoptosis rather than necrosis is considered as the dominant mechanism for neurodegeneration in PD (Reviewed in Kountouras et al., 2012). Furthermore, in a cellular model of PD, caspase-independent apoptosis has been shown even in the presence of cytochrome c release following complex I inhibition. However, the mechanism underlying pathogenesis of PD is still unknown. In addition to aging, epidemiological studies have introduced several factors that increase susceptibility to PD including pesticides, herbicides and industrial chemicals (Ascherio et al., 2006; Schapira, 2006).

Various genetic mutations have been found in familial forms of PD. The most common mutation occurs in dardarin/LRRK2 encoding gene (PARK8) that appears to be a member of multifunctional Ras/GTPase family (Zimprich et al., 2004). This research area is now a matter of strong scientific interest, as genetic factors have been found to play the key role in other diseases (Wiechec, 2011; Wiechec and Hansen, 2009). In situ hybridization-based studies displayed high expression of LRRK2 in dopamine-innervated areas in brains of both patients with PD and controls (Galter et al., 2006). The most convincing evidence for the role of LRRK2 in PD obtained from a cellular study that showed the

interaction of LRRK2 and death adaptor Fas-associated protein with death domain (FADD) resulted in the switching-on of the extrinsic apoptotic pathway via caspase-8 activation (Ho et al., 2009). Another recent study on the human neural stem cells pointed to the damaging effect of mutant LRRK2 on nuclear envelope that may be a causative factor in pathogenesis of PD, but they reported no evidence of apoptosis (Liu et al., 2012).

Aggregation of wild-type and mutant forms of α -syn in Lewy bodies is a hallmark of α -synucleinopathies like PD. These aggregates have been detected throughout the nervous system (Galvin et al., 1999). Alpha-syn seems to act as a molecular chaperone for SNARE synaptic proteins (Burre et al., 2010; Chandra et al., 2005). Increased level and accumulation of mutated α -syn in transgenic mice caused paralyzes and death (Giasson et al., 2002). A dopaminergic neuronal cell study revealed that α -syn can downregulate expression of PRC- δ , a proapoptotic oxidative stress-sensitive kinase, which suppress apoptosis in these cells (Jin et al., 2011). This finding seems to be in contrast with outcomes of the other cellular studies performed on SH-SY5Y neuroblastoma cells that showed overexpression of α -syn aggravated manganese induced apoptosis (Li et al., 2010).

Mutations in PARK2 gene that encodes parkin protein are a potent risk factor for PD. (Kitada et al., 1998). Parkin works as an ubiquitin E3 ligase with α -syn being one of its substrates. Therefore, mutation in this protein can result in accumulation of its substrates including α -syn (Yamamoto et al., 2005). Suppression of parkin in a cellular model of PD was accompanied by accumulation of Peal-R, another substrate of parkin. This causes accumulation of unfolded proteins in the ER and consequently increased rate of apoptosis (Zou et al., 2012). Parkin and its partner PIKN1, a mitochondrial kinase, co-work in a pathway to control mitochondria morphology and functionality (Geisler et al., 2010; Lazarou et al., 2012). Mounting evidences imply that PINK1 has a role in Ca^{2+} efflux in mitochondria. Deficiencies in PINK1 result in accumulation of Ca^{2+} in mitochondria and increased generation of ROS followed by opening mPTP and elevation in the rate of cell death (Akundi et al., 2011; Gandhi et al., 2009; Heeman et al., 2011; Marongiu et al., 2009).

DJ-1 is another mitochondrial protein with protective effects, partly ascribed to its function as an oxidative stress-induced chaperon (Zhou et al., 2006). DJ-1 mutations are associated with familial PD (Bonifati et al., 2003). A dopaminergic cell study attributed this neuroprotective effect of DJ-1 to its activating effect of the ERK pathway that results in mitophagy induction (Gao et al., 2012). DJ-1, PINK1 and parkin all are localized in mitochondria that suggest strong linkage of PD with mitochondrial dysfunction. Indeed, when mitochondria encounter an insult that makes it defective, reduction in membrane potential makes it targeted by PINK1 and parkin for mitophagy, a phenomenon that prevent apoptosis when insult is not so deleterious (Schapira, 2012; Youle and van der Bliek, 2012).

Existence of a strong link between ER stress and induction of apoptosis has been previously demonstrated (Nakagawa et al., 2000; Puthalakath et al., 2007). Recent evidences however, point to beneficial effects of mild ER stress on cell survival. Protective effects of ER stress induced by H_2O_2 have been shown in an in vitro study (Pallepati and Averill-Bates, 2011). Consistently, in animal and cellular model studies of PD ER stress has had neuroprotective effects by induction of autophagy (Fouillet et al., 2012; Matus et al., 2012).

16.3. Excitotoxicity-triggered apoptosis and other effects of mutated huntingtin protein in Huntington's disease

Much evidence supports the role of apoptosis in neurodegeneration observed in HD (Sawa et al., 1999; Vis et al., 2005;

Wellington et al., 2000a). However, in comparison to other neurodegenerative disease, few direct studies have been done in this area. Caspases (i.e. caspase-6) proteolytically cleave Htt (Kim et al., 2001; Wellington et al., 2000b) and release an N-terminal fragment containing the pQ motif, thus generating toxic mHtt fragments (Ratovitski et al., 2007). Overexpression of wild-type Htt had a protective effect in transgenic mice model of HD, by preventing NMADRs excitotoxicity (Leavitt et al., 2006).

Several mechanisms have been suggested to explain induction of apoptosis in HD. In a YAC transgenic HD mouse model, excitotoxicity mediated by glutamate NMDA receptors lead to intracellular calcium elevation, mitochondrial dysfunction and finally apoptosis in a pQ length-dependent manner (Shehadeh et al., 2006). Along these lines, another *in vivo* study reported increased extrasynaptic NMDA receptor expression as well as associated reductions in nuclear CREB activation in striatum of HD mouse. These changes correlated with mutation severity, were dependent on the cleavage of mHtt by caspase-6, and resulted in manifestation of the disease (Milnerwood et al., 2010). The exact link between Htt, caspase cleavage, and caspase activation patterns in the pathogenesis of HD is poorly understood, however, the activation of caspase-6, but not caspase-3, occurs before onset of mobility abnormalities in human and murine HD brain.

Inositol hexakisphosphate kinases (InsP(6)Ks) has been proposed as another apoptosis triggering factor, at least in a cellular models of AD. InsP(6)Ks promote apoptosis in a caspase-independent manner. Under stress conditions, an isoform of InsP6Ks, Inositol hexakisphosphate kinase type 2 (InsP(6)K2), mediates apoptotic cell death via its translocation from the nucleus to the cytoplasm. While InsP(6)K2 is localized in the nucleus of normal lymphoblasts, this enzyme is observed mainly in the cytoplasm of HD lymphoblast cells. This finding may suggests a role for InsP6K2 activation in the pathogenesis of HD (Nagata et al., 2010).

Huntingtin interacting protein (HIP-1) also contributes to induction of caspase-dependent apoptosis when its death-effector domain interacts with mHtt. Subsequent interaction of HIP-1 with its molecular partner HIPPI launches apoptosis (Gervais et al., 2002; Hackam et al., 2000). Whereas coexpression of HIP-1 and wild-type Htt reduces proapoptotic effect of HIP-1 (Choi et al., 2006). Findings of other studies however, imply that HIP-1 may act as an antiapoptotic factor in some experimental models (Bradley et al., 2007a, 2007b).

16.4. Amyotrophic lateral sclerosis and the role of apoptosis in the onset and progression of the disease

A spectrum of PCD have been shown in ALS using animal- and cellular models as well as postmortem tissues (Reviewed in Martin and Liu, 2004). Studies on spinal cord of SOD1 G93A transgenic mice and the most common mutations found in familial forms of ALS, revealed activation and translocation of AIF from mitochondria to the nucleus of motor neurons (Oh et al., 2006). Nuclear localization of AIF leads to induction of chromatin condensation, DNA fragmentation and finally caspase-independent apoptosis (Daugas et al., 2000). Tanaka and colleagues used a mice model of ALS to show that AIF and cyclophilin A co-translocate to the nucleus and cause motor neuron death (Tanaka et al., 2011).

In ALS, specific degeneration of motor neurons is associated with dysregulation of intracellular Ca^{2+} and excitotoxicity. These events point to the role of mitochondrial dysfunction and apoptosis. However, no strong and direct evidence has been found yet in human ALS pathophysiology that such events are important for the onset and/or progression of the disease. Muscle biopsy analysis revealed an increase in the intracellular level of Ca^{2+} and mitochondrial volume in motor nerve terminals of ALS patients as

compared to control groups (Siklos et al., 1996). In a case-control study, measurement of mitochondrial membrane potential of platelets, revealed severe depolarization of mitochondrial membrane and apoptosis in platelets of ALS patients as compared to controls (Shrivastava et al., 2011).

Glutamate-mediated excitotoxicity is another possible mechanism that is proposed in the pathogenesis of ALS (Reviewed in Rowland and Shneider, 2001). Motor neurons are more susceptible to glutamate excitotoxicity because of low GluR2 number or decrease in RNA editing of AMPA receptors on their surface, that make them vulnerable to elevated Ca^{2+} entry and mitochondrial impairment (Kwak and Kawahara, 2005). Pathological studies showed that increase in intracellular Ca^{2+} level leads to elevation of ROS production in mitochondria by activating mitochondrial permeability transition (Hansson et al., 2008). Low expression of calcium binding proteins in some subpopulations of motor neurons decreases their Ca^{2+} buffering capacity and makes them more susceptible to excitotoxicity (Reviewed in Bogaert et al., 2010). With this regard, “toxic shift of calcium” has been proposed as a new hypothesis influencing motor neuron death in ALS. This hypothesis offers a Ca^{2+} cycle between ER and mitochondria that maintains Ca^{2+} homeostasis in motor neurons (Reviewed in Grosskreutz et al., 2010).

The role of X-Box binding protein-1 (XBP-1) in ALS pathophysiology has recently been proposed. XBP-1 works in UPR pathway as a transcription factor. Results of a study on a mice model of ALS that is deficient in XBP-1, showed that the observed increase in mitophagy was associated with a decline in protein aggregation and disease progression (Matus et al., 2009). This finding implies that cross-talk may exist between UPR-autophagy pathways. On the other hand, treatment of SOD1 G93A mice with rapamycin made mitochondrial abnormalities worse. Bax level elevation and caspase-3 activation culminated in more motor neuron degeneration via apoptosis, a finding that suggests an impairment of autophagy pathway in this model of ALS (Zhang et al., 2011).

Strong evidence obtained from a longitudinal analysis proposed that different responses to ER stress in subpopulations of motor neurons affect the manifestation and progression of ALS (Saxena et al., 2009). In mutated superoxide dismutase (mSOD1) mice, accumulation of mSOD1 resulted in ER stress. Accumulating data suggest that ER stress may activate the mitochondrial apoptotic pathway resulting in the release of cytochrome c from the mitochondria (Heath-Engel et al., 2008; Hetz, 2007). ER stress occurs early in pathogenesis of ALS in SOD1 G93A transgenic mice (Atkin et al., 2006). Further studies have demonstrated that proapoptotic BH3-only proteins, Bim or Puma, are required for ER stress-induced apoptosis (Reimertz et al., 2003; Schapira, 2012). Bim is implicated in the molecular processes associated with pathology and cell death in transgenic mice expressing SOD1 G93A (Hetz et al., 2007). Bim appears to be the intermediary between ER stress and mitochondrial apoptosis in cells containing potentially toxic mSOD1 proteins (Soo et al., 2012). This finding validates the data regarding the ER stress-induced apoptosis action of CHOP on the expression of multiple pro-apoptotic BH3-only proteins in neuronal cells (Ghosh et al., 2012) (Table 2).

17. Connection between age-related neurodegenerative disorders and cell aging/cell senescence

Numerous studies suggest that age related neurodegenerative disorders cause cell aging and cell senescence and the latter might eventually lead to apoptosis or other forms of cell death. For instance, as the age of the human beings progress there is an increase in the production of reactive oxygen species and hence causing oxidative damage to nucleic acids especially RNA (Nunomura et al., 2012). This has been demonstrated in neurons

of human and rodent brains. In patients suffering from neurodegenerative disorders such as AD, PD, and ALS, there is a prominent increase in the neuronal RNA damage when compared to normal aging people (Nunomura et al., 2012). Oxidative RNA modification occurs not only in RNA that makes proteins but also in non coding RNA leading to aberrant expression of microRNAs and proteins that initiate cellular pathways and ultimately leading to cell death (Nunomura et al., 2012). In another study it has been shown that telomere, which is a repetitive DNA structure present at the end of the chromosomes becomes shorter with aging because of the defect in replication process (Maeda et al., 2012). The telomere shortening is accelerated in brain-associated illnesses such as in PD. The peripheral leukocytes of Japanese female patients with PD have fewer large telomeres and an increase in the hypomethylated subtelomeres in short telomeres when compared to the healthy control patients (Maeda et al., 2012). These results indicate that pathogenesis associated with neurodegenerative disorders could increase the structural changes in the telomeres thereby causing cells with smaller telomeres to die quickly (Maeda et al., 2012). Thus, from these evidences one could argue that drugs that delay the aging process could also prevent or at least postpone the age related disease such as neurodegenerative disorders. Numerous studies have shown that caloric restriction delays aging-induced phenotypes in a variety of species such as rats, mice, flies and primates (Blagosklonny, 2012). Furthermore, it has been demonstrated that inhibition of mTOR pathway extends the life span of yeast, flies and mice (Blagosklonny, 2012).

18. The potential of autophagy- and apoptosis modulation as a treatment strategy in neurodegenerative diseases

In previous paragraphs, we have highlighted the effects of autophagy and apoptosis on the etiology, and/or progression of neurodegenerative diseases. Below, we discuss how autophagy or apoptosis modulation may therapeutically affect the progress of those diseases.

18.1. Autophagy modulation and Huntington's diseases treatment strategies

There are no effective treatments that would reverse the neurodegeneration caused by HD. pQ expanded Htt aggregates accumulate in the brain and cause intraneuronal inclusions that result in neuronal loss and thereby cortical degeneration. Reduction of the content of mutant Htt aggregates can decrease the harmful effects caused by this disease. The Htt aggregates are degradable by autophagy. Although, macroautophagy cannot degrade nuclear inclusions (Iwata et al., 2009), some studies have found that autophagy is activated by Htt accumulation in the cytoplasm of striatal cells and participate in the degradation of Htt (Qin et al., 2003). Further studies confirmed the role of autophagy in the elimination of pQ repeats-carrying fragments (Ravikumar et al., 2002) and reduction of its toxicity (Liang et al., 2011). Hence, it has been demonstrated in cell models, transgenic mouse and human brain that the aggregated pQ proteins in the inclusions sequester mTOR. Sequestration of mTOR impairs its kinase activity and induces autophagy (Ravikumar et al., 2004). A recent study showed that rilmenidine, an anti-hypertensive drug induced autophagy in HD model mice and also in primary neuronal cell cultures (Rose et al., 2010). Administration of this drug attenuated signs of HD in mice models and also reduced aggregates of mutant Htt (Rose et al., 2010). Thus, rilmenidine can be considered as a drug for the treatment of HD and related conditions. Another recent study provided evidence that overexpression of full-length Huntington protein lacking pQ stretch in HD mice model significantly reduced the mutant Htt aggregates and also extended

Table 2

List of some of the potential apoptotic drugs used for treatment of neurodegenerative diseases.

Drug	Mechanism of action	References
Minocycline	It prevents release of cytochrome c from mitochondria Increases the expression anti-apoptotic protein Bcl-2 and inhibits the activity of caspases-1 and -2	Kim and Suh (2009) and Seidl and Potashkin (2011)
CEP-1347	Inhibits the mixed lineage kinase (MLK) family, thereby preventing apoptosis	Wang et al. (2004)
Rasagiline	Selective and irreversible inhibitor of MAO-B	Youdim et al. (2005)
	Inhibits apoptosis by activating protein kinase C and by down regulating FAS and Bax family of proteins	
Selegiline	Selective inhibitor of MAO-B	Tatton and Chalmers-Redman (1996)
	Inhibits apoptosis by up-regulating regulating Bcl-2 protein	
	Minimize loss of mitochondrial potential	
	Inhibit the activity of caspases	
Coenzyme Q 10	Protect neurons from oxidative stress by scavenging reactive oxygen species	Choi et al. (2012)
Melatonin	It is a chemical compound secreted by pineal gland	Pandi-Perumal et al. (2012)
	Prevents the oxidative stress by stimulating the synthesis of antioxidant enzymes such as super oxide dismutase and glutathione peroxidase	
Resveratrol	A chemical compound present in grapes, red wine and other fruits.	Khan et al. (2010)
	Inhibits the oxidative stress by up regulating the anti-oxidant system	
Lithium	It rescues spinal cord mitochondria in ALS	Pandi-Perumal et al. (2012)
	Facilitates the clearance of SOD1 and ubiquitin in ALS motor neurons	

the lifespan of HD mice when compared to the control HD mice (Zheng et al., 2010). Mice carrying over-expressed HD also showed normal lipofuscin levels in the brain and also an increased steady level of autophagy. Thus, upregulation of autophagy can expand the life span of HD mice by clearing out aggregates containing mutated Htt (Zheng et al., 2010).

Small molecule enhancers of rapamycin (SMERs) augment autophagy and therefore have therapeutic potential in the treatment of various neurodegenerative disorders such as HD and PD (Floto et al., 2007). However rapamycin's side effects such as immuno-suppression at early stages of treatment prevented its use in treating neurodegenerative diseases. Three SMERs, which act independently of mTOR pathway, have been identified (Floto et al., 2007). These SMERs clear the mutated Htt in HD cell models and extended the lifespan of the cells (Floto et al., 2007). So SMERs, which act independently of the mTOR pathway, could be used as therapeutic molecules in treatment of degenerative diseases.

18.2. Alzheimer's diseases – autophagy modulation as therapy approach

Large accumulation of autophagosomes in dystrophic neuritis was observed in the animal models of AD and in postmortem brains of AD patients. Dysfunction in macroautophagy may enhance γ -secretase activity, which in turn increases A β by cleaving amyloid- β precursor protein (APP) (Ohta et al., 2010). Furthermore, the AD drug (galanthamine hydrochloride) shows inhibitory effects on autophagy (Lipinski et al., 2010), suggesting that decreased formation of autophagosomes may decline levels of A β (Lipinski et al., 2010). These findings confirm conclusions from other studies that autophagosome may be an intracellular A β reservoir which form when maturation of autophagosomes to autolysosomes is impaired (Yu et al., 2005). Moreover, despite autophagy is downregulated in the normal aging brains (Lipinski et al., 2010), it is transcriptionally upregulated in the brains of AD patients (Lipinski et al., 2010). This may be a way to compensate for the deficit in UPS (Korolchuk et al., 2010). In contrast, beclin-1 (ATG6) level, a key component for autophagosome formation in the autophagy canonical pathway, is reduced in affected brain regions of AD patients (Pickford et al., 2008). Defects in the autophagy and accumulation of autophagosomes are attributed to the decreased in expression of beclin-1. Hence, induction of autophagy using small molecules that can critically regulate autophagy can be a better therapeutic target for controlling AD.

Resveratrol is a phenolic compound abundant in red wine, grapes, and numerous fruits. Because of its antioxidative and anti-inflammatory properties it is widely used as an alternative therapy for various pathologies including cardiovascular diseases and cancer. As mentioned previously, in the course of various neurodegenerative disorders, including AD, the excessive production of reactive oxygen species in brain could be observed. The reactive oxygen species-scavenging properties of resveratrol indicate that it could be used as a therapeutic agent in afore mentioned pathologies. Neuritic plaques composed mainly of A β in the brain are an early and invariant neuropathological feature of AD (Ono et al., 2006). Resveratrol lowers the levels of secreted and intracellular A β peptides produced by various cell lines (Marambaud et al., 2005). The A β -lowering effect of resveratrol relies not on the inhibition of A β production, but on the promotion of its intracellular degradation via proteasome-based mechanism. This was shown in experiments where resveratrol-induced decrease of A β , could be prevented by proteasome-selective inhibitors. These findings demonstrate a proteasome-dependent anti-amyloido-genic activity of resveratrol, and suggest that this natural compound has a therapeutic potential in AD (Marambaud et al., 2005). In other studies, the phytochemical resveratrol and its analogous (RSVA314 and RSVA405) have shown potent stimulatory effects on autophagy and A β clearance (Vingtdeux et al., 2011). It seems that resveratrol effects are mediated by its impact on the AMPK signaling pathway that controls A β metabolism (Vingtdeux et al., 2010). However, these effects of the resveratrol may also be partly attributed to the increased levels of neurotrophic factors (Rahvar et al., 2011). This phytochemical may induce BDNF expression, and ameliorate synaptic degeneration and memory deficits in an transgenic (Tg2576) mouse model of AD (Iwasaki et al., 2012). In animal model of AD and tau pathology, resveratrol reduced neurodegeneration in hippocampus, abrogated the learning deficit, and decreased the acetylation of SIRT1 substrates PGC-1 α and p53 (Kim et al., 2007). Resveratrol is presently in phase II clinical trials for treating patients with mild to moderate AD.

Lithium, a compound used as a mood stabilizer, is neuroprotective in many of the disease models (Fornai et al., 2008). Thus, daily administration of lithium in human Alzheimer patients delayed disease progression. Apart from that, in a genetic mouse model of Alzheimer disease, lithium treatment induced a marked neuroprotection, as well as a delayed progress of the disease along with an increase in the lifespan of the animals (Fornai et al., 2008). Such effects were concomitant with activation of autophagy and an

increase in the number of the mitochondria in neurons and suppressed reactive astrogliosis (Fornai et al., 2008). These results showed promising evidence for lithium as a drug for the treatment of AD.

18.3. Parkinson's disease – therapeutic effect of autophagy

As mentioned earlier, PD is a neurodegenerative disorder marked by loss of dopaminergic neurons in the brain-stem and the presence of intraneuronal inclusions designated as Lewy bodies (Lee et al., 2009). Overexpression of α -syn in the neuronal cells can lead to lysosomal accumulation and alterations in autophagy (Spencer et al., 2009). Expression of beclin-1 in cells that overexpress α -syn reduced accumulation of α -syn in these cells and rescued them from lysosomal accumulation and alterations in autophagy (Spencer et al., 2009). Introduction of *beclin-1* gene into the brain of α -syn transgenic mice ameliorated the synaptic and dendritic pathology and enhanced lysosomal activation and reduced alterations in the autophagy pathway. These results provide evidence that beclin-1 can be a novel therapeutic target for the treatment of PD (Spencer et al., 2009).

Trehalose is a non-reducing disaccharide present in many organisms and it induces autophagy (Sarkar et al., 2007). Trehalose induced autophagy enhanced the clearance of mutant forms of both α -syn and huntingtin. These results provide the evidence that trehalose can be used as a small molecule in the treatment of neurodisorders like PD (Sarkar et al., 2007).

18.4. Apoptosis modulation and neurodegenerative diseases treatment strategy

Minocycline, a member of tetracycline-family of antibiotics, inhibits apoptosis by preventing oxidative stress, blocks the release of cytochrome *c* from mitochondria and disrupts the activation of caspase-3 (Kim and Suh, 2009). It also increases the expression of anti-apoptotic protein Bcl-2 and inhibits the expression of caspases-1 and -2 (Kim and Suh, 2009). Because of its role as an anti-apoptotic molecule it is tested in several models of neurodegenerative disorders such as HD, AD and PD. In all these animal models it prevented the aggravation of disease by reducing apoptosis. In small clinical trials minocycline was proven effective in treatment of PD and AD (Ono et al., 2006). Hence, minocycline is now in phase II and phases III clinical trials for several other diseases such as spinal cord injury and stroke.

CEP-1347 is an inhibitor of Mixed Lineage Kinase (MLK) family of kinases. These kinases potentiate neuronal cell death signal transduction pathway. So inhibiting this pathway can be a good therapeutic target in prevention of various neurodegenerative diseases. Experimental evidence shows that CEP-1347 prevents apoptosis in neurons by inhibiting MLK family of kinases (Wang et al., 2004). In one clinical study, the researchers performed a randomized, blind, placebo-controlled study assessing the safety, tolerability, pharmacokinetics, and acute symptomatic effects of CEP-1347 in 30 patients with PD (Wang et al., 2004). In this short-term study, CEP-1347 was proven to be safe and well tolerated in the patients with PD (Wang et al., 2004). However, a larger clinical study proved that CEP-1347 is not effective for treating the patients who suffer from PD (2007).

Rasagiline (*N*-propargyl-1R-aminoindan) is a selective and irreversible inhibitor of monoamine oxidase B (MAO-B). MAO-B catalyzes breakdown of dopamine in brain by releasing hydrogen peroxide, which is in part responsible for the oxidative damage in PD. In neuronal cells, rasagiline inhibited apoptosis induced by neurotoxins by preventing the mitochondrial permeability transition and by up-regulating anti-apoptotic Bcl-2 proteins (Maruyama et al., 2002). Their neuroprotective effects are also due

to activation of protein kinase C and by downregulating apoptosis inducer molecules such as Fas and Bax (Youdim et al., 2005). In the first clinical study in 2002, rasagiline was used as treatment option for PD and was more effective in the patients with early PD (2002). In one of the recent clinical studies involving rasagiline (ADAGIO study), the early treatment with 1 mg per day dosage showed benefits, however 2 mg per day dosage did not have the same effect (Olanow et al., 2009). Because the two doses were associated with different outcomes, the study results must be interpreted with caution (Olanow et al., 2009). In an extension of ADAGIO, study authors randomly selected 1176 patients with untreated early PD and investigated effect of rasagiline 1 mg or 2 mg per day for 72 weeks (early-start group) (Rascol et al., 2011). Another group was treated with placebo for 36 weeks followed by 1 mg or 2 mg per day for next 36 weeks (delayed-start group). From these studies, authors concluded that rasagiline delayed the need for symptomatic antiparkinsonian drugs and improved (unified PD rating scale) UPDRS ADL (daily living activities) scores, an effect clearly visible during the placebo-controlled phase of the studies (Rascol et al., 2011).

Selegiline is another selective inhibitor for MAO-B, which is similar to rasagiline that also exhibits anti-apoptotic activity. Selegiline treatment decreases both the oxidative and nutritive stress by lowering the H_2O_2 overproduction as well as diminishes the amount of reactive oxygen- and nitrogen species (Tipton et al., 2004). Superoxide anion radicals can react with nitric oxide (NO) and form peroxy nitrate, which spontaneously decomposes to OH^- and NO_2 (Tipton et al., 2004). Pretreatment with selegiline can protect neurons against a variety of neurotoxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-hydroxydopamine, *N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine (DSP-4), methyl-beta-acetoxyethyl-2-chloroethylamine (AF64A), and 5,6-dihydroxyserotonin, which damage dopaminergic, adrenergic, cholinergic, and serotonergic neurons, respectively (Ebadi et al., 2002). Selegiline reduces the production of reactive oxygen species, upregulates superoxide dismutase and catalase, and suppresses nonenzymatic, iron-catalyzed auto-oxidation of dopamine. It delays apoptosis in serum-deprived cells, and blocks apoptosis-related fall in the mitochondrial membrane potential (Ebadi et al., 2002). The protective action of selegiline against apoptosis can be attributed to the upregulation of Bcl-2 proteins (Tatton and Chalmers-Redman, 1996). Selegiline is currently in clinical trials for the treatment of PD (Ondo et al., 2011).

Coenzyme Q10 is another compound currently considered as a potential experimental drug for the treatment of neurodegenerative diseases. Coenzyme Q10 resides in the inner mitochondrial membrane as a part of electron transport chain and participates in aerobic respiration. Many of the neurodegenerative disorders are characterized by defects in the inner mitochondrial membrane and in oxidative phosphorylation (Camins et al., 2010). Coenzyme Q10 is shown to protect neurons from oxidative stress. Recently, a multicenter, clinical study tested nanoparticulate coenzyme Q10 for the treatment of PD-patients (Storch et al., 2007). The study concluded that nanoparticulate coenzyme Q10 at a dosage of 300 mg/day is safe and well tolerated and leads to plasma levels similar to 1200 mg/day dosage of a standard formulation. Coenzyme Q10 applied in such doses and the nanoparticulate formulation does not cause side effects in mid-stage PD (Storch et al., 2007). Coenzyme Q10 was also clinically tested on patients with HD (Shults, 2003).

Melatonin, which is secreted in a circadian rhythm-regulated manner by pineal gland in mammalian brain, has ROS scavenging activity. Because of its anti-oxidative function it can be tested as an experimental drug in neurodegenerative diseases with ROS involvement. Its mechanism of action could be attributed to stimulating the synthesis of antioxidant enzymes including

superoxide dismutase, glutathione peroxidase, glutathione reductase, and augmenting glutathione level (Pandi-Perumal et al., 2012). Melatonin preserves mitochondrial homeostasis, reduces free radical generation and protects mitochondrial ATP synthesis by stimulating Complexes I and IV activities (Pandi-Perumal et al., 2012). In one of the animal trials conducted on melatonin in murine ALS model (SOD1(G93A)-transgenic mice), it delayed disease progression and extended survival (Weishaupt et al., 2006). Furthermore the authors showed that in a clinical safety study long-term high-dose of 300 mg/day melatonin applied per rectum was well tolerated during an observation period of up to 2 years. Importantly, circulating serum protein carbonyls, which provide a surrogate marker for oxidative stress, were elevated in ALS patients, but were normalized to control values by melatonin treatment (Weishaupt et al., 2006). This combination of preclinical effectiveness and proven safety in humans suggests that high-dose melatonin treatment should be tested in clinical trials aimed at neuroprotection in ALS. Melatonin also has protective effects in HD. In a recent study, using R6/2 transgenic-mouse HD model, the authors demonstrated that melatonin delayed disease onset and prolonged life span of mice (Wang et al., 2011b). Hence, melatonin receptor MT1 levels decrease in cultured striate cells, mouse brain, and human striatum associated with mutant Htt-mediated toxicity, and receptor depletion becomes greater as the disease progresses. Melatonin administration counteracted MT1 receptor depletion in experimental models utilizing mutant-Htt, both in vitro and in vivo (Wang et al., 2011b). These results indicate that melatonin should be clinically tested for the HD therapy.

Melatonin is also effective in protecting the transgenic mice with AD. Long-term administration of melatonin orally protected the mice from cognitive deficits and abrogated the rise of markers of neurodegeneration (Olcese et al., 2009). Furthermore, melatonin's cognitive protection likely involved three complementary mechanisms: (i) counteracting A β aggregation, (ii) anti-inflammatory actions/immunomodulation, and (iii) normalization of antioxidant defenses (Olcese et al., 2009). Protective effect of melatonin in PD models as also been recently reported (Wang, 2009).

Besides melatonin, in one recent study, using the 6-hydroxydopamine induced PD rat model, authors demonstrated that resveratrol upregulated the antioxidant defenses and lowered the dopamine loss (Khan et al., 2010). Elevated level of thiobarbituric acid reactive substances (TBARS), protein carbonyl (PC), and activity of phospholipase A2 was attenuated significantly in resveratrol pretreated animals (Khan et al., 2010). Hence, resveratrol may be used to reduce the deterioration caused by free radicals thereby preventing subsequent behavioral, biochemical, and histopathological changes that occur during PD (Khan et al., 2010).

Other potential drugs such as valproic acid, isradipine and lithium might be used to treat various neurodegenerative disorders (Khan et al., 2010). Additionally, Hurperzine A, an alkaloid from Chinese herb and a compound found in *Ginkgo biloba* called EGb, both have anti-apoptotic properties and are tested in treating various neurodegenerative disorders (Khan et al., 2010).

19. Closing remarks

Neurodegenerative disorders are common, prevalent ailments of senior years, and they become increasingly widespread as society's members' age advances. These diseases are devastating not only due to their economic impact on the society (costs of healthcare, loss of productivity, etc.), but also because they literally rob individuals from their identity. Thus, despite societies around the world invest billions of dollars in the search for drugs that would stop, or at least significantly slow-down neurodegeneration,

the results are unsatisfactory at best. Therefore, it is important to search for new targets that may be pharmacologically engaged, to curb the progress of neurodegenerative diseases. As outlined above, much attention in recent years attracted experimental drugs that modulate autophagy and/or apoptosis. While the several promising experimental anti-neurodegenerative drugs have been developed, one has to exercise some caution with respect to autophagy modulating drugs. Modulation of autophagy alone will likely not result in satisfactory clinical effects. This is because of the very interconnected nature of autophagy, as well as due to the fact that while a low level of autophagy would generally promote cell survival; extensive autophagy may actually kill the targeted cell (Chaabane et al., 2013). Therefore, as shown on some examples in previous paragraphs, autophagy-modulating anti-degenerative drugs, when clinically implemented, would most likely show desired results when their pro-survival effects are strengthened by conjoined therapies.

Modulation of some autophagy- and apoptosis regulators has to be done with caution, particularly due to the interconnected nature of both processes. Some targets like, i.e. the prosurvival kinase Akt, affect both autophagy and apoptosis. It blocks autophagy both via Foxo3 inhibition and mTOR activation (Jain et al., 2013). Cytoplasmic Akt acts as a prosurvival kinase, whereas when in the nucleus it may contribute to cell death induction (Maddika et al., 2008). The effects of nuclear Akt on autophagy are so far largely unknown. While modulators of autophagy and apoptosis may offer some "quick fixes" for diseases with neurodegenerative background, the long term solutions in this area will likely be worked out based on regenerative medicine (Hombach-Klonisch et al., 2008) and tissue-engineering approaches.

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