**IMPACTS OF AUTOPHAGY AND APOPTOSIS DYSFUNCTION IN ALZHEIMER’S DISEASE**

**BY**

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**DEPARTMENT OF HUMAN ANATOMY**

**Autophagy**

Autophagy (from the Greek, “auto” oneself, “phagy” to eat) refers to any cellular degradative pathway that involves the delivery of cytoplasmic cargo to the lysosome (EisenbergLerner et al., 2009). At least three forms have been identified chaperone-mediated autophagy, microautophagy, and macroautophagy that differ with respect to their physiological functions and the mode of cargo delivery to the lysosome. Autophagy principally serves an adaptive role to protect organisms against diverse pathologies, including infections, cancer, neurodegeneration, aging, and heart disease.

However, in certain experimental disease settings, the self-cannibalistic or, paradoxically, even the prosurvival functions of autophagy may be deleterious.

**Apoptosis**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). 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 effecter caspases.

**Alzheimer’s disease (AD)**

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 b-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 g-secretase-mediated processes by PSEN1 and PSEN2, the neurotoxic peptide amyloid-b (Ab) is formed (Nizzari *et al*., 2007; Sotthibundhu *et al*., 2008; Vila and Przedborski, 2003). Abnormal levels of extracellular Ab-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 g-secretase activity, although the definitive pathway is yet to be determined. Furthermore, indications of variations in the genes encoding insulin-degrading enzyme (IDE) and ubiquilin-1 (UBQLN1), involved in Ab degradation and intracellular trafficking of APP respectively, have been reported (Minati *et al*., 2009).

**Disturbed Autophagy on Alzheimer’s disease**

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 Ab and a-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 (Zn2+) supplementation improved mitochondrial function and ameliorated hippocampal Ab and tau pathogenic signs in a mouse model of AD. Notably, dietary Zn2+ supplementation reduced intraneuronal Ab, 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).

Macroautophagy is transcriptionally up-regulated (Lipinski et al., 2010) Autophagosome maturation is impaired (Yu et al., 2005) Macroautophagy is inhibited by mutated presinilin-1 in a familial form of AD (Cataldo et al., 2004)

Chaperon-mediated autophagy degrades regulator of calcineurin- 1 (RCAN1) (Liu et al., 2009) CMA degrades Tau proteins (Wang, 2009)

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 g-secretase activity, which in turn increases Ab by cleaving amyloid-b 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 Ab (Lipinski *et al*., 2010). These findings confirm conclusions from other studies that autophagosome may be an intracellular Ab 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.

**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, Ab peptide, will overload. Toxic effect of Ab is manifested by ROS generation, apoptosis induction and impaired memory (Lustbader *et al*., 2004). Although most deleterious effects of Ab is attributed to Ab deposits (Abramov *et al*., 2004; Picone *et al*., 2009), extracellular Ab (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 Ab impairs mitochondria metabolism by decreasing cytochrome oxidase activity and increasing hydrogen peroxide generation (Manczak *et al*., 2006). Moreover, Ab 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 Ab (Cecconi *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 Ab peptide (Fossati *et al*., 2012). Ab 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 Ab 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 Ca2+ regulation (Resende *et al*., 2008a,b). The E693d mutation in APP in transfected HEK293 and COS-7 cells caused accumulation of Ab in ER, subsequent increased ER stress markers, such as Grp78 and phosphorylated eIF2a, and finally stress-induced apoptosis in the ER (Nishitsuji *et al*., 2009).

Apoptosis modulation and Alzheimer’s disease 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 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.

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