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Review

Role of Mitochondrial Amyloid-β in Alzheimer's Disease

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Abstract. Mitochondrial dysfunction is an early feature of Alzheimer's disease (AD). Abnormalities in mitochondrial properties include impaired energy metabolism, defects in key respiratory enzyme activity/function, accumulation/generation of mitochondrial reactive oxygen species, and formation of membrane permeability transition pore. While the mechanisms underlying mitochondrial dysfunction remain incompletely understood, recent studies provide substantial evidence for the progressive accumulation of mitochondrial Aβ, which directly links to mitochondria-mediated toxicity. In this review, we describe recent studies addressing the following key questions: 1) Does Aβ accumulate in mitochondria of AD brain and AD mouse models? 2) How does Aβ gain access to the mitochondria? 3) If mitochondria are loaded with Aβ, do they develop similar evidence of dysfunction? 4) What are the mechanisms underlying mitochondrial Aβ-induced neuronal toxicity? and 5) What is the impact of interaction of mitochondrial Aβ with its binding partners (cyclophilin D and ABAD) on mitochondrial and neuronal properties/function in an Aβ milieu? The answers to these questions provide new insights into mechanisms of mitochondrial stress related to the pathogenesis of AD and information necessary for developing therapeutic strategy for AD.

Keywords: Alzheimer's disease, amyloid, cyclophilin, mitochondria, toxicity

INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative disease, resulting in a disorder of cognition and memory due to neuronal stress and culminating in cell death. Genetic, cell biology, biochemical, and animal studies support the concept that amyloid-β (Aβ) plays a central role in the development of AD pathology and neuronal and cognitive malfunction. Mutations in genes for amyloid-β precursor protein (AβPP) and presenilins (PS1 and PS2) result in rare, early-onset AD due to enhanced generation and accumulation of Aβ [1–3]. Growing evidence indicates that early intracellular accumulation of Aβ may be a key factor in the induction of neuronal stress. Aβ is generated intracellularly and has been shown to accumulate intracellularly. In addition, AβPP/Aβ moves from the endoplasmic reticulum (ER) to the trans-Golgi network, or the endosomal-lysosomal system. The presence of intracellular Aβ has been detected in brains of patients with AD and Down's syndrome as well as in aging monkeys and transgenic (Tg) mice expressing mutant AβPP [4–7]. Furthermore, the accumulation of intracellular Aβ has been shown to precede plaque formation in Tg mutant AβPP/PS1 and Tg mutant AβPP/PS1/tau mice, and is associated with neuronal loss even in the absence of extracellular Aβ deposits [8–10]. Accumulation of intracellular Aβ increases with age, is associated with abnormal synaptic morphology, and correlates with the deficits in long-term synaptic plasticity. These

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observations led us to consider a role of intracellular Aβ. Notably, recent studies have highlighted the role of mitochondrial Aβ in AD pathogenesis [11–28].

Mitochondria have a crucial role in both necrotic and apoptotic cell death. Mitochondrial dysfunction is an early feature of AD. Abnormalities of mitochondrial function [13,19,29], such as decreased activity of respiratory chain enzymes, generation of reactive oxygen species (ROS), and hypometabolism occur in the AD brain and the Tg AD mouse models [12–15,22,30–46]. These observations suggest a potentially important role for mitochondria in determining the abnormalities of AD brain. Mitochondria may be a central player for Aβ-induced impairment of neuronal energetic and oxidative damage contributing importantly to the neuronal perturbation in AD. In this review, we summarize and discuss the role of mitochondrial Aβ in mitochondrial and neuronal stress in an environment enriched for Aβ, such as AD and Tg mouse models for AD.

ACCUMULATION OF Aβ IN CORTICAL MITOCHONDRIA OF AD BRAIN

Studies from our and other independent groups have clearly demonstrated that Aβ progressively accumulates within mitochondria of AD brain [13,15,20,21, 23], Tg AD mice, and cells overexpressing mutant human AβPP and Aβ [13–15,18,20,23,26]. First, immunoblotting studies revealed the presence of Aβ in highly purified human brain mitochondria, which displayed enrichment of mitochondrial markers SODII and cytochrome c oxidase and the apparent absence of markers for endoplasmic reticulum and lysosomes. Second, we performed a protease protection assay to determine whether Aβ was present within mitochondria (i.e., within a membrane-enclosed compartment) or adsorbed to the outer mitochondrial membrane. After permeabilizing mitochondrial membranes with Triton X-100, trypsin treatment nearly completely prevented the appearance of immunoreactive Aβ, indicating that most mitochondria-associated Aβ was in a protected, membrane-bound compartment [13]. Third, to further establish the localization of Aβ in mitochondria, we performed morphological studies to support the results of the biochemical experiments. Both confocal microscopy and immunoelectron microscopy studies, using double immunostaining of anti-Aβ and a mitochondrial marker, reveal the colocalization of Aβ with mitochondrial markers. Based on image analysis, Aβ accumulates in the mitochondria of AD brain with $\sim$40% and $\sim$70% of the area occupied by mitochondria in the temporal lobe and hippocampus, respectively, co-staining for the Aβ. The non-AD control brains also showed accumulation of Aβ in mitochondria, but at lower levels, corresponding to 5% and 14% of the area occupied by mitochondria in the temporal lobe and hippocampus, respectively. Furthermore, mitochondrial localization of Aβ has been found in human cortical brains in surgical specimens obtained from living subjects that showed amyloidosis similar to the extent of mitochondrial Aβ accumulation [21]. Thus, these studies have firmly established the accumulation of mitochondrial Aβ in Aβ-rich brain, such as AD.

Accumulation of mitochondrial Aβ also occurs in Tg mouse models for AD. Accumulation of Aβ in mitochondria occurs as early as 4-5 months and increases with aging in brains of Tg mAβPP mice [13]. The latter finding indicates that Aβ starts to accumulate in mitochondria even before massive extracellular deposition occurs. This observation is in agreement with previous findings that intracellular accumulation of Aβ can occur prior to extracellular amyloid β accumulation [10, 47,48]. Notably, levels of mitochondrial Aβ_{42} were significantly higher than Aβ_{40} ($\sim$4-5 folds higher versus Aβ_{40}). In addition, oligomeric Aβ_{42} was also found in the mitochondria from AD brain and Tg mAβPP mice. These results indicate the pathogenic role of mitochondrial Aβ, predominately the 1-42 form, in abnormal mitochondrial function relevant to the pathogenesis of AD. Consistent with our findings, mitochondrial Aβ has also been reported in other lines of Tg AD mouse model (Tg2576) [14,26,43]. Further, Aβ accumulates in mitochondria of primary neuronal cultured neurons from Tg mAβPP mice, as shown by confocal and electron microscopy and immunoblotting of subcellular fractions. These findings add a new dimension to studies of intracellular Aβ, particular for mitochondrial Aβ.

MITOCHONDRIAL Aβ UPTAKE

The progressive accumulation of Aβ in mitochondria raises a question: how does Aβ gain access to mitochondria? Aβ is generated by the sequential intracellular cleavage of AβPP by β-secretase to generate the N-terminal end of Aβ, and intramembranous cleavage by γ-secretase to generate the C-terminal end. Further studies have shown that Aβ is generated within the trans-Golgi network or produced within ER, and then translocated to the endosomal/lysomal system or

the cytosolic fraction [49–51]. The detectable amount of Aβ is normally retained within the cell. These intracellular pools of Aβ can also be released to the extracellular space via the plasma membrane. Another possible source of intracellular Aβ is the reuptake of extracellular Aβ through receptor-dependent mechanism [52,53], endosomal/lysomal or unknown pathway [21]. These studies suggest the significance of the regulation/modulation of the balance in Aβ pool between intracellular and extracellular compartments under pathophysiological condition.

To determine whether mitochondrial Aβ is produced *in situ* by mitochondria or by uptake from intracellular compartment, we first examined the mitochondrial localization of AβPP. Immunoblotting with antibody specific for human form of AβPP or human and mouse AβPP, demonstrated no immunoreactive band in digitonin-treated mitochondria enriched for Aβ from AβPP mice (Yan et al., unpublished observation), indicating that AβPP is not present inside mitochondria. Anandatheerthavarada and colleagues recently reported that AβPP is targeted to the mitochondrial outer membrane in an "N-terminus-in mitochondria and C-terminus-out cytoplasm" orientation and is associated with mitochondrial import channels. Although generation of mitochondrial Aβ could be due to the cleavage of AβPP with the N-terminus targeted to the mitochondrial membrane through γ-secretase that has been identified within the mitochondria, the ability of γ-secretase to cleave AβPP associated with mitochondria is not known. The absence of AβPP within mitochondria and delayed appearance of mitochondrial Aβ, as reported in our study, suggest that mitochondrial Aβ is not likely to be produced locally in mitochondria and a complex cellular trafficking system is involved in importing Aβ into mitochondria.

The following studies support this concept that mitochondrial Aβ is derived from extracellular or intracellular pool of Aβ. First, Petersen and colleagues presented a unique import mechanism for Aβ in mitochondria and demonstrate both *in vitro* and *in vivo* that Aβ is transported into mitochondria via the translocase of the outer membrane (TOM) machinery [21]. Importantly, they demonstrated extracellular applied Aβ can be internalized by human neuroblastoma cells, imported into mitochondria via the TOM complex, and accumulated in the mitochondrial cristae. Second, Takuma and collaborators showed that receptor for advanced glycation end products (RAGE) contributes to the transport of Aβ from cell surface to the intracellular space [52]. Mouse cortical neurons exposed to extracellular human Aβ subsequently show detectable Aβ peptide intracellularly in the cytosol and mitochondria by confocal and electron microscopy.

Blockade of RAGE by RAGE antibody or RAGE-deficiency significantly decreases the uptake of Aβ and provides protection from Aβ-mediated mitochondrial dysfunction. These findings indicate the involvement of RAGE in the translocation of Aβ from the extracellular to the intracellular compartment including mitochondria. Third, we propose that Aβ is able to directly translocate from the ER to the mitochondria in view of the direct contact/communication of ER membrane to the mitochondrial out membrane. To address this issue, we performed an *in vitro* translocation assay. Purified subfractions of ER/Golgi from brains of Tg mAβPP mice with detectable human Aβ were incubated with mitochondria isolated from non-Tg brains with no human form of Aβ. Aβ was subsequently found in purified mitochondria of non-Tg mice incubated with ER/Golgi fractions from Tg mAβPP mice (Yan et al., unpublished data). Furthermore, when Aβ-containing neurons cultured from Tg mAβPP mice were incubated with brefeldin A, an inhibitor of protein transport from ER/intermediate compartment [54], levels of Aβ were increased in mitochondrial fractions. These results suggest that Aβ is imported into intact mitochondria, potentially via the secretory pathway (ER/Golgi). Abnormalities in the secretory pathway may trigger a pathologic accumulation of Aβ in mitochondria.

IMPACT OF Aβ ON MITOCHONDRIAL AND NEURONAL FUNCTION

Another key issue concerns whether accumulation of mitochondrial Aβ interferes with respiratory and/or other functions of this organelle potentially modulating cellular properties. Patients with AD are known to display diminished glucose utilization, abnormal brain energetics and reduced activity of certain enzymes associated with mitochondrial respiratory chain complexes [30,33,36,38,39,41,55]. In addition, mitochondria are well-recognized for their role in the generation of ROS and in mediating cell death signals. First, we studies metabolic properties of Tg mAβPP mice by evaluating brain ATP levels and glucose utilization. At 10 months, there was a significant decrease in ATP in the brains of Tg mAβPP mice compared with non-Tg littermates. Glucose utilization was studied using NMR by infusing mice with ^{13}C-labelled glucose, and analyzing the flux of acetyl coenzyme A through the

TCA (trichloroacetic acid/Krebs) cycle. There was a statistically significant decrease in glucose uptake and in the flux of acetyl coenzyme A through the TCA cycle in the brains of Tg mAβPP mice [12]. Second, respiratory rate, as assessed by oxygen consumption and membrane potential, was significantly reduced in mitochondria from Tg mAβPP mice as compared with non-Tg mice, enzymatic activities associated with mitochondrial complex III (cytochrome c reductase) and IV (cytochrome c oxidase) were significantly decreased in mitochondria from Tg mAβPP mice, as compared with non-Tg mice [13,23–25]. Similar results were observed in human AD brain as described above. Third, Aβ-rich cortical mitochondria isolated from Tg mAβPP mice showed increases in accumulation of ROS in mitochondria, mitochondrial membrane potential and mitochondrial membrane permeability transition, and a decrease in calcium buffering capacity [15,23,24]. Consequences of Aβ-mediated mitochondrial dysfunction were seen by regional changes in neuropathology and impaired spatial learning memory in Tg mAβPP mice as compared with those in non-Tg littermate controls [15,23,24,56,57]. These data suggest that, in an Aβ-rich environment, overt mitochondrial dysfunction occurs and that mitochondria provide a direct site for Aβ-mediated cellular perturbation. For instance, increased expression of amyloid binding alcohol dehydrogenase (ABAD), an intracellular Aβ-binding protein, exacerbated mitochondrial and neuronal stress in hAβPP/Aβ expressing mice [12,15]. Aβ can also directly disrupt mitochondrial function and such disruption causes oxidative stress [58,59]. Thus, impairments in mitochondrial structure and function could be due to the direct effect of Aβ or through interaction of Aβ with its binding partners, which exaggerates mitochondrial and neuronal perturbation.

INTERACTION OF Aβ WITH ITS MITOCHONDRIAL TARGETS

The mitochondrial permeability transition pore (mPTP) plays a central role in both necrotic and apoptotic neuronal cell death. Opening of the mPTP collapses the membrane potential and amplifies apoptotic mechanisms by releasing proteins with apoptogenic potential from inner membrane space [60–62]. The mPTP is thought to involve, at least, the voltage dependent anion channel (VDAC) in the outer membrane, the adenine nucleotide translocase (ANT) in the inner membrane, and cyclophilin D (CypD) in the mitochondrial matrix [61,63–66]. CypD, a peptidylprolyl isomerase F (gene name: Ppif), resides in the mitochondrial matrix and associates with the inner mitochondrial membrane during the mPTP. Release of CypD from the matrix allows it to bind to ANT, and potentially to other targets on the inner mitochondrial membrane. This interaction contributes to opening the mPTP, which leads to colloidosmotic swelling of the mitochondrial matrix, dissipation of the inner membrane potential ($\Delta\Psi_m$), and/or generation of ROS. Therefore, CypD is an integral part of the mPTP complex. Oxidative and other cellular stresses promote CypD translocation to the inner membrane [67–72], which in turn triggers opening of the mPTP. The ultimate consequence of opening pore is the release of intermembrane space-located proteins, including cytochrome c, apoptosis inducing factor, Smac/DIABLO, endonuclease G, and procaspases [73–77]. In turn, these proteins will activate signal transduction pathways and apoptosis, causing cell death. Moreover, recent studies provide substantial evidence that a genetic deficiency in CypD protects cells from Ca^{2+}- and oxidative stress-induced cell death, indicating that CypD functions as a necessary component of the mPTP [71,78–80]. Low expression of CypD in brain mitochondria increases resistance of mPT induced by calcium [81], whereas high levels of CypD in neuronal mitochondria result in their greater vulnerability to mPTP and require higher levels of cyclosporin (an inhibitor of CypD) to inhibit mPTP opening [82]. We have demonstrated that levels of CypD were significantly elevated in Aβ-containing cortical mitochondria from AD-affected brain regions of patients with AD and Tg mAβPP mice. Using surface plasmon resonance (SPR), we have found that CypD binds immobilized Aβ in a dose-dependent manner. CypD formed a complex with Aβ in cortical mitochondria from AD patients and Tg mAβPP mice. An increased CypD translocation from the matrix to the inner membrane of mitochondria was observed in Tg mAβPP mice compared to non-Tg littermates. Most importantly, abrogation of CypD significantly attenuates Aβ-mediated abnormal mitochondrial and neuronal dysfunction, improves long term potentiation (LTP) and learning memory. The protection of CypD deficiency occurs in aged mAβPP mice (22-24 months) that express florid amyloid pathology and severe cognitive decline [24]. These data demonstrate that the lack of CypD results in persistent life-long protection against Aβ toxicity in an AD mouse model, thereby suggesting that inhibiting CypD may be benefit for prevention and treatment of AD.

ABAD is an intracellular enzyme present in the mitochondrial matrix. Initially, using the yeast two-

hybrid system, and, subsequently, by ligand binding assays with purified polypeptides, our group identified ABAD as a single chain, ≈27 kDa polypeptide capable of binding Aβ [83] (Note: we initially termed this Aβ binding polypeptide ERAB, but have changed the name to ABAD in view of its functional properties, see below). ABAD is a member of the short-chain dehydrogenase/reductase (SDR) family, which has broad enzymatic activity [84–90]. Though members of the SDR family have overlapping enzymatic properties, ABAD appears to have essential functions, especially during development, as mutational inactivation of the Drosophila counterpart (termed *scully*) resulted in a lethal phenotype [91]. It has been reported that analysis of 2-methy-3-hydroxybutyryl-CoA dehydrogenase (MHBD) deficiency (associated with abnormal catabolism of isoleucine and branched chain fatty acids) resulted from two missense mutations in the ABAD gene [92]. The unique feature of ABAD, compared to other members of the SDR family, is its interaction with Aβ [15,83,93].

In the absence of high levels of Aβ, under homeostatic or stressful conditions, ABAD appears to exert a protective role in the cellular response [86]. For example, ABAD facilitates utilization of ketone bodies by promoting the generation of acetyl-CoA to feed into the TCA cycle. Using NMR to analyze [^{13}C] β-hydroxybutyrate metabolism, ABAD-transfected COS cells displayed increased flux of acetyl-CoA through the TCA cycle. Because ischemia is a severe metabolic stress, a murine stroke model was employed to determine the consequences of overexpressing ABAD in cortical neurons. Tg mice overexpressing ABAD in neurons demonstrated a protective phenotype with a ∼40% reduction in stroke volume and improved neurologic deficit scores. Overexpression of ABAD in Tg mice was associated with increased flux of acetyl-CoA through the TCA cycle and increased ATP in cerebral cortex following infusion of β-hydroxybutyrate. These data indicate that the expression of ABAD confers a protective phenotype in the setting of ischemia. Taken together, these properties of ABAD suggested its attractiveness, in terms of potential for cellular perturbation, as an intracellular target of Aβ.

In an Aβ-rich environment,we have shown that ABAD potentiates cell stress induced by Aβ, as evidenced by the increased generation of 4-hydroxynonenal-lysine (HNE) and malondialdehyde (MDA)-lysine epitopes, induction of DNA fragmentation, and generation of ROS (as detected by electron paramagnetic resonance spectroscopy, in cells overexpressing ABAD and mutant AβPP[V717G] and in Tg mice) [15, 83,84]. Furthermore, double Tg mice overexpressing ABAD and a mutant form of the human amyloid precursor protein (mAβPP; the latter a minigene encoding hAβPP695, 751 & 770 bearing mutations linked to familiar AD) show regional neuropathologic changes (decreased synaptophysin and acetylcholinesterase activity) in the cortex and hippocampus. Consequences of such neuropathologic changes include impaired spatial memory and reduced LTP in double Tg mice overexpressing ABAD and mutant AβPP in neurons.In support of our data, results from other laboratories have shown that the interaction of ABAD with Aβ accentuated cytotoxicity, which was attenuated by blockade of ABAD engagement of Aβ. Furthermore, high levels of ABAD have been found in hippocampal synaptic mitochondria from Tg mutant AβPP mice, and this has been suggested to contribute to the loss of synapses in the hippocampus observed in this animal model of AD-type pathology [94–98]. Increased expression of ABAD has also been found in mitochondrial from other Tg AD mouse models [43,99]. The expression levels of ABAD correlate with mitochondrial Aβ levels. Importantly, ABAD expression levels are significant higher in AD-affected brain regions (inferior temporal gyrus and hippocampus) than those in age-matched, non-AD brain [15]. Regions spared by AD, such as cerebellum, displayed no significant difference in ABAD expression comparing AD and non-AD brains. Similarly, Tg mAβPP mice show higher level of ABAD (∼2-3 fold) in hippocampus and cerebral cortex than non-Tg controls. These results, demonstrating increased expression of ABAD in AD brain, support the potential relevance of ABAD to Aβ-induced neuronal stress.

To further analyze mechanisms and consequences of ABAD-Aβ interaction, we have performed structural studies and experiments using genetically manipulated mice. Our most recent data analyzing Aβ-ABAD crystals suggests that residues 94-114 of ABAD interact with Aβ. A peptide spanning this region of ABAD inhibits ABAD-Aβ interaction *in vitro*. Most importantly, ABAD [91–119] peptide protected neurons harvested from either wild-type, single Tg (overexpressing mAβPP or ABAD) or double Tg (overexpressing ABAD and mAβPP) mice from Aβ-induced cytotoxicity. These data support the premise that ABAD-Aβ interaction is not only a key factor in the potentiation Aβ-induced cytotoxicity, but also may be an effective target for therapeutic intervention in AD. Abnormalities in oxidative/energy metabolism are closely associated with AD. Defects in mitochondrial func-

tion are well-known to contribute to alterations in energy metabolism, free radical generation, and cellular calcium homeostasis [30,31,33,100–105]. Our studies in double Tg mice have shown enhanced generation of ROS in double Tg mice overexpressing mutant AβPP and ABAD (Tg mAβPP/ABAD) at 4 months of age compared with controls. These Tg mice also display upregulation of peroxiredoxin II[106], an antioxidant protein, and endophilin-1 [42] protein relevant to JNK-mediated cell death signal transduction pathway. Consistent with this observation, defects in energy metabolism (reduced levels of ATP and decreased glucose utilization) and activation of CAMK II were noted in double Tg mice (mAβPP/ABAD). These factors, potentially impacting on and/or due to mitochondrial dysfunction, could lead to neuronal damage in AD.

Finally, since ABAD is localized principally to the mitochondrial matrix in neurons, it was essential to determine if ABAD and Aβ actually interacted in pathophysiologically-relevant settings. Aβ was identified within mitochondria and evidence of ABAD-Aβ complex could be demonstrated by immunoprecipitation-immunoblotting in brains of AD patients and Tg mAβPP mice. The activity of cytochrome c oxidase (COX, complex IV) was significantly reduced (∼40%) in mitochondria from Tg mAβPP/ABAD mice, compared with single Tgs (Tg mAβPP, Tg ABAD) and non-Tg littermates, as early as 4 months of age. This observation in a mouse model of AD-type pathology is consistent with decreased COX activity previously noted in AD brain [33,100], suggesting that formation ABAD-Aβ complex may be responsible for this and other changes in mitochondrial properties.

CONCLUSION

Mitochondria are a central player in cell death relevant to the pathogenesis of many neurodegenerative diseases, such as AD. Mitochondrial dysfunction is an early feature of AD and Aβ has deleterious effects on mitochondrial function and contributes to energy failure, respiratory chain impairment, neuronal apoptosis, and the generation of ROS in AD. Recent studies have highlighted the role of mitochondrial Aβ in the pathogenesis of AD. Extracellular or intracellular Aβ is able to transport into the mitochondria through receptor-dependent pathway, TOM40 machinery, direct ER-mitochondria transfer, or other unknown mechanisms. The progressive accumulation of mitochondrial Aβ is associated with aberrant mitochondrial function leading to neuronal damage and cognitive decline. In this regard, Aβ can directly affect mitochondrial respiratory enzyme activity and trigger mitochondrial membrane permeability transition pore opening. Interactions of Aβ and mitochondrial proteins (CypD and ABAD) exaggerate Aβ-induced effects on mitochondrial and neuronal function. Blocking Aβ binding to such partners protects against mitochondrial and neuronal toxicity. Thus, blocking Aβ entry to mitochondria, inhibiting CypD-dependent mitochondrial transition pore, or intercepting interaction of Aβ with binding partners, such as ABAD, are potential therapeutic strategies for AD.

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REFERENCES

[1] Hardy J (1997) Amyloid, the presenilins and Alzheimer's disease. *Trends Neurosci* **20**, 154-159.

[2] Sisodia SS, St George-Hyslop PH (2002) gamma-Secretase, Notch, Abeta and Alzheimer's disease: where do the presenilins fit in? *Nat Rev Neurosci* **3**, 281-290.

[3] George-Hyslop PS, Rossor M (2001) Alzheimer's disease. Unravelling the disease process. *Lancet* **358 Suppl**, S1.

[4] D'Andrea MR, Nagele RG, Wang HY, Peterson PA, Lee DH (2001) Evidence that neurones accumulating amyloid can undergo lysis to form amyloid plaques in Alzheimer's disease. *Histopathology* **38**, 120-134.

[5] Gouras GK, Tsai J, Naslund J, Vincent B, Edgar M, Checler F, Greenfield JP, Haroutunian V, Buxbaum JD, Xu H, Greengard P, Relkin NR (2000) Intraneuronal Abeta42 accumulation in human brain. *Am J Pathol* **156**, 15-20.

[6] Martin LJ, Pardo CA, Cork LC, Price DL (1994) Synaptic pathology and glial responses to neuronal injury precede the formation of senile plaques and amyloid deposits in the aging cerebral cortex. *Am J Pathol* **145**, 1358-1381.

[7] Martin BL, Schrader-Fischer G, Busciglio J, Duke M, Paganetti P, Yankner BA (1995) Intracellular accumulation of beta-amyloid in cells expressing the Swedish mutant amyloid precursor protein. *J Biol Chem* **270**, 26727-26730.

[8] Hsia AY, Masliah E, McConlogue L, Yu GQ, Tatsuno G, Hu K, Kholodenko D, Malenka RC, Nicoll RA, Mucke L (1999) Plaque-independent disruption of neural circuits in Alzheimer's disease mouse models. *Proc Natl Acad Sci U S A* **96**, 3228-3233.

[9] Li QX, Maynard C, Cappai R, McLean CA, Cherny RA, Lynch T, Culvenor JG, Trevaskis J, Tanner JE, Bailey KA, Czech C, Bush AI, Beyreuther K, Masters CL (1999) Intracellular accumulation of detergent-soluble amyloidogenic A beta fragment of Alzheimer's disease precursor protein in the hippocampus of aged transgenic mice. *J Neurochem* **72**, 2479-2487.

[10] Wirths O, Multhaup G, Czech C, Blanchard V, Moussaoui S, Tremp G, Pradier L, Beyreuther K, Bayer TA (2001) Intraneuronal Abeta accumulation precedes plaque formation in beta-amyloid precursor protein and presenilin-1 double-transgenic mice. *Neurosci Lett* **306**, 116-120.

[11] Reddy PH, Beal MF (2008) Amyloid beta, mitochondrial dysfunction and synaptic damage: implications for cognitive decline in aging and Alzheimer's disease. *Trends Mol Med* **14**, 45-53.

[12] Takuma K, Yao J, Huang J, Xu H, Chen X, Luddy J, Trillat AC, Stern DM, Arancio O, Yan SS (2005) ABAD enhances Abeta-induced cell stress via mitochondrial dysfunction. *FASEB J* **19**, 597-598.

[13] Caspersen C, Wang N, Yao J, Sosunov A, Chen X, Lustbader JW, Xu HW, Stern D, McKhann G, Yan SD (2005) Mitochondrial Abeta: a potential focal point for neuronal metabolic dysfunction in Alzheimer's disease. *FASEB J* **19**, 2040-2041.

[14] Manczak M, Anekonda TS, Henson E, Park BS, Quinn J, Reddy PH (2006) Mitochondria are a direct site of A beta accumulation in Alzheimer's disease neurons: implications for free radical generation and oxidative damage in disease progression. *Hum Mol Genet* **15**, 1437-1449.

[15] Lustbader JW, Cirilli M, Lin C, Xu HW, Takuma K, Wang N, Caspersen C, Chen X, Pollak S, Chaney M, Trinchese F, Liu S, Gunn-Moore F, Lue LF, Walker DG, Kuppusamy P, Zewier ZL, Arancio O, Stern D, Yan SS, Wu H (2004) ABAD directly links Abeta to mitochondrial toxicity in Alzheimer's disease. *Science* **304**, 448-452.

[16] Reddy PH (2006) Amyloid precursor protein-mediated free radicals and oxidative damage: implications for the development and progression of Alzheimer's disease. *J Neurochem* **96**, 1-13.

[17] Shukkur EA, Shimohata A, Akagi T, Yu W, Yamaguchi M, Murayama M, Chui D, Takeuchi T, Amano K, Subramhanya KH, Hashikawa T, Sago H, Epstein CJ, Takashima A, Yamakawa K (2006) Mitochondrial dysfunction and tau hyperphosphorylation in Ts1Cje, a mouse model for Down syndrome. *Hum Mol Genet* **15**, 2752-2762.

[18] Hirai K, Aliev G, Nunomura A, Fujioka H, Russell RL, Atwood CS, Johnson AB, Kress Y, Vinters HV, Tabaton M, Shimohama S, Cash AD, Siedlak SL, Harris PL, Jones PK, Petersen RB, Perry G, Smith MA (2001) Mitochondrial abnormalities in Alzheimer's disease. *J Neurosci* **21**, 3017-3023.

[19] Lin MT, Beal MF (2006) Alzheimer's APP mangles mitochondria. *Nat Med* **12**, 1241-1243.

[20] Devi L, Prabhu BM, Galati DF, Avadhani NG, Anandatheerthavarada HK (2006) Accumulation of amyloid precursor protein in the mitochondrial import channels of human Alzheimer's disease brain is associated with mitochondrial dysfunction. *J Neurosci* **26**, 9057-9068.

[21] Hansson Petersen CA, Alikhani N, Behbahani H, Wiehager B, Pavlov PF, Alafuzoff I, Leinonen V, Ito A, Winblad B, Glaser E, Ankarcrona M (2008) The amyloid beta-peptide is imported into mitochondria via the TOM import machinery and localized to mitochondrial cristae. *Proc Natl Acad Sci U S A* **105**, 13145-13150.

[22] Yao J, Irwin RW, Zhao L, Nilsen J, Hamilton RT, Brinton RD (2009) Mitochondrial bioenergetic deficit precedes Alzheimer's pathology in female mouse model of Alzheimer's disease. *Proc Natl Acad Sci U S A* **106**, 14670-14675.

[23] Du H, Guo L, Fang F, Chen D, Sosunov AA, McKhann GM, Yan Y, Wang C, Zhang H, Molkentin JD, Gunn-Moore FJ, Vonsattel JP, Arancio O, Chen JX, Yan SD (2008) Cyclophilin D deficiency attenuates mitochondrial and neuronal perturbation and ameliorates learning and memory in Alzheimer's disease. *Nat Med* **14**, 1097-1105.

[24] Du H, Guo L, Zhang W, Rydzewska M, Yan S (2009) Cyclophilin D deficiency improves mitochondrial function and learning/memory in aging Alzheimer disease mouse model. *Neurobiol Aging*, in press.

[25] Du H, Yan SS (2009) Mitochondrial permeability transition pore in Alzheimer's disease: Cyclophilin D and amyloid beta. *Biochim Biophys Acta* **1802**, 198-204.

[26] Crouch PJ, Blake R, Duce JA, Ciccotosto GD, Li QX, Barnham KJ, Curtain CC, Cherny RA, Cappai R, Dyrks T, Masters CL, Trounce IA (2005) Copper-dependent inhibition of human cytochrome c oxidase by a dimeric conformer of amyloid-beta1-42. *J Neurosci* **25**, 672-679.

[27] Yamaguchi H, Yamazaki T, Ishiguro K, Shoji M, Nakazato Y, Hirai S (1992) Ultrastructural localization of Alzheimer amyloid beta/A4 protein precursor in the cytoplasm of neurons and senile plaque-associated astrocytes. *Acta Neuropathol* **85**, 15-22.

[28] Mungarro-Menchaca X, Ferrera P, Moran J, Arias C (2002) beta-Amyloid peptide induces ultrastructural changes in synaptosomes and potentiates mitochondrial dysfunction in the presence of ryanodine. *J Neurosci Res* **68**, 89-96.

[29] Swerdlow RH (2009) The neurodegenerative mitochondriopathies. *J Alzheimers Dis* **17**, 737-751.

[30] Beal MF (2004) Mitochondrial dysfunction and oxidative damage in Alzheimer's and Parkinson's diseases and coenzyme Q10 as a potential treatment. *J Bioenerg Biomembr* **36**, 381-386.

[31] Blass JP (2000) The mitochondrial spiral. An adequate cause of dementia in the Alzheimer's syndrome. *Ann N Y Acad Sci* **924**, 170-183.

[32] Chen X, Stern D, Yan SD (2006) Mitochondrial dysfunction and Alzheimer's disease. *Curr Alzheimer Res* **3**, 515-520.

[33] Maurer I, Zierz S, Moller HJ (2000) A selective defect of cytochrome c oxidase is present in brain of Alzheimer disease patients. *Neurobiol Aging* **21**, 455-462.

[34] Cottrell DA, Blakely EL, Johnson MA, Ince PG, Turnbull DM (2001) Mitochondrial enzyme-deficient hippocampal neurons and choroidal cells in AD. *Neurology* **57**, 260-264.

[35] Cottrell DA, Borthwick GM, Johnson MA, Ince PG, Turnbull DM (2002) The role of cytochrome c oxidase deficient hippocampal neurones in Alzheimer's disease. *Neuropathol Appl Neurobiol* **28**, 390-396.

[36] de la Monte SM, Luong T, Neely TR, Robinson D, Wands JR (2000) Mitochondrial DNA damage as a mechanism of cell loss in Alzheimer's disease. *Lab Invest* **80**, 1323-1335.

[37] Mutisya EM, Bowling AC, Beal MF (1994) Cortical cytochrome oxidase activity is reduced in Alzheimer's disease. *J Neurochem* **63**, 2179-2184.

[38] Parker WD, Jr., Parks J, Filley CM, Kleinschmidt-DeMasters BK (1994) Electron transport chain defects in Alzheimer's disease brain. *Neurology* **44**, 1090-1096.

[39] Parker WD, Jr., Mahr NJ, Filley CM, Parks JK, Hughes D, Young DA, Cullum CM (1994) Reduced platelet cytochrome

c oxidase activity in Alzheimer's disease. *Neurology* **44**, 1086-1090.
[40] Parker WD, Jr. (1991) Cytochrome oxidase deficiency in Alzheimer's disease. *Ann N Y Acad Sci* **640**, 59-64.
[41] Valla J, Berndt JD, Gonzalez-Lima F (2001) Energy hypometabolism in posterior cingulate cortex of Alzheimer's patients: superficial laminar cytochrome oxidase associated with disease duration. *J Neurosci* **21**, 4923-4930.
[42] Ren Y, Xu HW, Davey F, Taylor M, Aiton J, Coote P, Fang F, Yao J, Chen D, Chen JX, Yan SD, Gunn-Moore FJ (2008) Endophilin I expression is increased in the brains of Alzheimer disease patients. *J Biol Chem* **283**, 5685-5691.
[43] Yao J, Irwin RW, Zhao L, Nilsen J, Hamilton RT, Brinton RD (2009) Mitochondrial bioenergetic deficit precedes Alzheimer's pathology in female mouse model of Alzheimer's disease. *Proc Natl Acad Sci U S A* **106**, 14670-14675.
[44] Crouch PJ, Harding SM, White AR, Camakaris J, Bush AI, Masters CL (2008) Mechanisms of A beta mediated neurodegeneration in Alzheimer's disease. *Int J Biochem Cell Biol* **40**, 181-198.
[45] Anandatheerthavarada HK, Biswas G, Robin MA, Avadhani NG (2003) Mitochondrial targeting and a novel transmembrane arrest of Alzheimer's amyloid precursor protein impairs mitochondrial function in neuronal cells. *J Cell Biol* **161**, 41-54.
[46] Wang X, Su B, Lee HG, Li X, Perry G, Smith MA, Zhu X (2009) Impaired balance of mitochondrial fission and fusion in Alzheimer's disease. *J Neurosci* **29**, 9090-9103.
[47] Mori C, Spooner ET, Wisniewsk KE, Wisniewski TM, Yamaguch H, Saido TC, Tolan DR, Selkoe DJ, Lemere CA (2002) Intraneuronal Abeta42 accumulation in Down syndrome brain. *Amyloid* **9**, 88-102.
[48] Glabe C (2001) Intracellular mechanisms of amyloid accumulation and pathogenesis in Alzheimer's disease. *J Mol Neurosci* **17**, 137-145.
[49] Hartmann T, Bieger SC, Bruhl B, Tienari PJ, Ida N, Allsop D, Roberts GW, Masters CL, Dotti CG, Unsickr K, Beyreuther K (1997) Distinct sites of intracellular production for Alzheimer's disease A beta40/42 amyloid peptides. *Nat Med* **3**, 1016-1020.
[50] Cook DG, Forman MS, Sung JC, Leight S, Kolson DL, Iwatsubo T, Lee VM, Doms RW (1997) Alzheimer's A beta(1-42) is generated in the endoplasmic reticulum/intermediate compartment of NT2N cells. *Nat Med* **3**, 1021-1023.
[51] Greenfield JP, Tsai J, Gouras GK, Hai B, Thinakaran G, Checler F, Sisodia SS, Greengard P, Xu H (1999) Endoplasmic reticulum and trans-Golgi network generate distinct populations of Alzheimer beta-amyloid peptides. *Proc Natl Acad Sci U S A* **96**, 742-747.
[52] Takuma K, Fang F, Zhang W, Yan S, Fukuzaki E, Du H, Sosunov A, McKhann G, Funatsu Y, Nakamichi N, Nagai T, Mizoguchi H, Ibi D, Hori O, Ogawa S, Stern DM, Yamada K, Yan SS (2009) RAGE-mediated signaling contributes to intraneuronal transport of amyloid-beta and neuronal dysfunction. *Proc Natl Acad Sci U S A* **106**, 20021-20026.
[53] El Khoury J, Hickman SE, Thomas CA, Cao L, Silverstein SC, Loike JD (1996) Scavenger receptor-mediated adhesion of microglia to beta-amyloid fibrils. *Nature* **382**, 716-719.
[54] Fujiwara T, Oda K, Yokota S, Takatsuki A, Ikehara Y (1988) Brefeldin A causes disassembly of the Golgi complex and accumulation of secretory proteins in the endoplasmic reticulum. *J Biol Chem* **263**, 18545-18552.
[55] Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE (1997) Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Ann Neurol* **42**, 85-94.
[56] Chen X, Stern, D, Yan SD (2007) Cellular targets of amyloid beta peptide: potential roles in neuronal cell stress and toxicity. In *Neurobiology of Alzheimer's disease*, Dawbarn D, Allen S, Eds. Oxford University Press, Oxford, pp. 227-243.
[57] Chen X, Yan SD (2006) Mitochondrial Abeta: a potential cause of metabolic dysfunction *in Alzheimer's disease. IUBMB Life* **58**, 686-694.
[58] Cardoso SM, Santana I, Swerdlow RH, Oliveira CR (2004) Mitochondria dysfunction of Alzheimer's disease cybrids enhances Abeta toxicity. *J Neurochem* **89**, 1417-1426.
[59] Cardoso SM, Santos S, Swerdlow RH, Oliveira CR (2001) Functional mitochondria are required for amyloid beta-mediated neurotoxicity. *FASEB J* **15**, 1439-1441.
[60] Crompton M (2004) Mitochondria and aging: a role for the permeability transition? *Aging Cell* **3**, 3-6.
[61] Halestrap AP, McStay GP, Clarke SJ (2002) The permeability transition pore complex: another view. *Biochimie* **84**, 153-166.
[62] Halestrap A (2005) Biochemistry: a pore way to die. *Nature* **434**, 578-579.
[63] Zamzami N, Larochette N, Kroemer G (2005) Mitochondrial permeability transition in apoptosis and necrosis. *Cell Death Differ* **12 Suppl 2**, 1478-1480.
[64] Crompton M, Barksby E, Johnson N, Capano M (2002) Mitochondrial intermembrane junctional complexes and their involvement in cell death. *Biochimie* **84**, 143-152.
[65] Halestrap AP (2006) Calcium, mitochondria and reperfusion injury: a pore way to die. *Biochem Soc Trans* **34**, 232-237.
[66] Bernardi P, Krauskopf A, Basso E, Petronilli V, Blachly-Dyson E, Di Lisa F, Forte MA (2006) The mitochondrial permeability transition from *in vitro* artifact to disease target. *Febs J* **273**, 2077-2099.
[67] Crompton M, Virji S, Ward JM (1998) Cyclophilin-D binds strongly to complexes of the voltage-dependent anion channel and the adenine nucleotide translocase to form the permeability transition pore. *Eur J Biochem* **258**, 729-735.
[68] Halestrap AP, Woodfield KY, Connern CP (1997) Oxidative stress, thiol reagents, and membrane potential modulate the mitochondrial permeability transition by affecting nucleotide binding to the adenine nucleotide translocase. *J Biol Chem* **272**, 3346-3354.
[69] Connern CP, Halestrap AP (1994) Recruitment of mitochondrial cyclophilin to the mitochondrial inner membrane under conditions of oxidative stress that enhance the opening of a calcium-sensitive non-specific channel. *Biochem J* **302** (**Pt 2**), 321-324.
[70] Andreeva L, Heads R, Green CJ (1999) Cyclophilins and their possible role in the stress response. *Int J Exp Pathol* **80**, 305-315.
[71] Baines CP, Kaiser RA, Purcell NH, Blair NS, Osinska H, Hambleton MA, Brunskill EW, Sayen MR, Gottlieb RA, Dorn GW, Robbins J, Molkentin JD (2005) Loss of cyclophilin D reveals a critical role for mitochondrial permeability transition in cell death. *Nature* **434**, 658-662.
[72] Pastorino JG, Chen ST, Tafani M, Snyder JW, Farber JL (1998) The overexpression of Bax produces cell death upon induction of the mitochondrial permeability transition. *J Biol Chem* **273**, 7770-7775.

[73] Liu X, Kim CN, Yang J, Jemmerson R, Wang X (1996) Induction of apoptotic program in cell-free extracts: requirement for dATP and cytochrome c. *Cell* **86**, 147-157.

[74] Zou H, Henzel WJ, Liu X, Lutschg A, Wang X (1997) Apaf-1, a human protein homologous to C. elegans CED-4, participates in cytochrome c-dependent activation of caspase-3. *Cell* **90**, 405-413.

[75] Susin SA, Lorenzo HK, Zamzami N, Marzo I, Brenner C, Larochette N, Prevost MC, Alzari PM, Kroemer G (1999) Mitochondrial release of caspase-2 and -9 during the apoptotic process. *J Exp Med* **189**, 381-394.

[76] Adrain C, Creagh EM, Martin SJ (2001) Apoptosis-associated release of Smac/DIABLO from mitochondria requires active caspases and is blocked by Bcl-2. *EMBO J* **20**, 6627-6636.

[77] Li LY, Luo X, Wang X (2001) Endonuclease G is an apoptotic DNase when released from mitochondria. *Nature* **412**, 95-99.

[78] Nakagawa T, Shimizu S, Watanabe T, Yamaguchi O, Otsu K, Yamagata H, Inohara H, Kubo T, Tsujimoto Y (2005) Cyclophilin D-dependent mitochondrial permeability transition regulates some necrotic but not apoptotic cell death. *Nature* **434**, 652-658.

[79] Basso E, Fante L, Fowlkes J, Petronilli V, Forte MA, Bernardi P (2005) Properties of the permeability transition pore in mitochondria devoid of Cyclophilin D. *J Biol Chem* **280**, 18558-18561.

[80] Schinzel AC, Takeuchi O, Huang Z, Fisher JK, Zhou Z, Rubens J, Hetz C, Danial NN, Moskowitz MA, Korsmeyer SJ (2005) Cyclophilin D is a component of mitochondrial permeability transition and mediates neuronal cell death after focal cerebral ischemia. *Proc Natl Acad Sci U S A* **102**, 12005-12010.

[81] Eliseev RA, Filippov G, Velos J, VanWinkle B, Goldman A, Rosier RN, Gunter TE (2007) Role of cyclophilin D in the resistance of brain mitochondria to the permeability transition. *Neurobiol Aging* **28**, 1532-1542.

[82] Hajnoczky G, Hoek JB (2007) Cell signaling. Mitochondrial longevity pathways. *Science* **315**, 607-609.

[83] Yan SD, Fu J, Soto C, Chen X, Zhu H, Al-Mohanna F, Collison K, Zhu A, Stern E, Saido T, Tohyama M, Ogawa S, Roher A, Stern D (1997) An intracellular protein that binds amyloid-beta peptide and mediates neurotoxicity in Alzheimer's disease. *Nature* **389**, 689-695.

[84] Yan SD, Shi Y, Zhu A, Fu J, Zhu H, Zhu Y, Gibson L, Stern E, Collison K, Al-Mohanna F, Ogawa S, Roher A, Clarke SG, Stern DM (1999) Role of ERAB/L-3-hydroxyacyl-coenzyme A dehydrogenase type II activity in Abeta-induced cytotoxicity. *J Biol Chem* **274**, 2145-2156.

[85] Powell AJ, Read JA, Banfield MJ, Gunn-Moore F, Yan SD, Lustbader J, Stern AR, Stern DM, Brady RL (2000) Recognition of structurally diverse substrates by type II 3-hydroxyacyl-CoA dehydrogenase (HADH II)/amyloid-beta binding alcohol dehydrogenase (ABAD). *J Mol Biol* **303**, 311-327.

[86] Du Yan S, Zhu Y, Stern ED, Hwang YC, Hori O, Ogawa S, Frosch MP, Connolly ES, Jr., McTaggert R, Pinsky DJ, Clarke S, Stern DM, Ramasamy R (2000) Amyloid beta - peptide-binding alcohol dehydrogenase is a component of the cellular response to nutritional stress. *J Biol Chem* **275**, 27100-27109.

[87] Kobayashi A, Jiang LL, Hashimoto T (1996) Two mitochondrial 3-hydroxyacyl-CoA dehydrogenases in bovine liver. *J Biochem* **119**, 775-782.

[88] Furuta S, Kobayashi A, Miyazawa S, Hashimoto T (1997) Cloning and expression of cDNA for a newly identified isozyme of bovine liver 3-hydroxyacyl-CoA dehydrogenase and its import into mitochondria. *Biochim Biophys Acta* **1350**, 317-324.

[89] He XY, Schulz H, Yang SY (1998) A human brain L-3-hydroxyacyl-coenzyme A dehydrogenase is identical to an amyloid beta-peptide-binding protein involved in Alzheimer's disease. *J Biol Chem* **273**, 10741-10746.

[90] Perez RG, Soriano S, Hayes JD, Ostaszewski B, Xia W, Selkoe DJ, Chen X, Stokin GB, Koo EH (1999) Mutagenesis identifies new signals for beta-amyloid precursor protein endocytosis, turnover, and the generation of secreted fragments, including Abeta42. *J Biol Chem* **274**, 18851-18856.

[91] Torroja L, Ortuno-Sahagun D, Ferrus A, Hammerle B, Barbas JA (1998) scully, an essential gene of Drosophila, is homologous to mammalian mitochondrial type II L-3-hydroxyacyl-CoA dehydrogenase/amyloid-beta peptide-binding protein. *J Cell Biol* **141**, 1009-1017.

[92] Ofman R, Ruiter JP, Feenstra M, Duran M, Poll-The BT, Zschocke J, Ensenauer R, Lehnert W, Sass JO, Sperl W, Wanders RJ (2003) 2-Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency is caused by mutations in the HADH2 gene. *Am J Hum Genet* **72**, 1300-1307.

[93] Yan Y, Liu Y, Sorci M, Belfort G, Lustbader JW, Yan SS, Wang C (2007) Surface plasmon resonance and nuclear magnetic resonance studies of ABAD-Abeta interaction. *Biochemistry* **46**, 1724-1731.

[94] Oppermann UC, Salim S, Tjernberg LO, Terenius L, Jornvall H (1999) Binding of amyloid beta-peptide to mitochondrial hydroxyacyl-CoA dehydrogenase (ERAB): regulation of an SDR enzyme activity with implications for apoptosis in Alzheimer's disease. *FEBS Lett* **451**, 238-242.

[95] Milton NG, Mayor NP, Rawlinson J (2001) Identification of amyloid-beta binding sites using an antisense peptide approach. *Neuroreport* **12**, 2561-2566.

[96] Shuli S, Yongmei Z, Zhiwei Z, Zhijuan J (2001) beta-Amyloid and its binding protein in the hippocampus of diabetic mice: effect of APP17 peptide. *Neuroreport* **12**, 3317-3319.

[97] He XY, Wen GY, Merz G, Lin D, Yang YZ, Mehta P, Schulz H, Yang SY (2002) Abundant type 10 17 beta-hydroxysteroid dehydrogenase in the hippocampus of mouse Alzheimer's disease model. *Brain Res Mol Brain Res* **99**, 46-53.

[98] Wen GY, Yang SY, Kaczmarski W, He XY, Pappas KS (2002) Presence of hydroxysteroid dehydrogenase type 10 in amyloid plaques (APs) of Hsiao's APP-Sw transgenic mouse brains, but absence in APs of Alzheimer's disease brains. *Brain Res* **954**, 115-122.

[99] Chen JX, Yan SD (2007) Amyloid-beta-induced mitochondrial dysfunction. *J Alzheimers Dis* **12**, 177-184.

[100] Sheehan JP, Swerdlow RH, Miller SW, Davis RE, Parks JK, Parker WD, Tuttle JB (1997) Calcium homeostasis and reactive oxygen species production in cells transformed by mitochondria from individuals with sporadic Alzheimer's disease. *J Neurosci* **17**, 4612-4622.

[101] Bosetti F, Brizzi F, Barogi S, Mancuso M, Siciliano G, Tendi EA, Murri L, Rapoport SI, Solaini G (2002) Cytochrome c oxidase and mitochondrial F1F0-ATPase (ATP synthase) activities in platelets and brain from patients with Alzheimer's disease. *Neurobiol Aging* **23**, 371-376.

[102] Davis RE, Miller S, Herrnstadt C, Ghosh SS, Fahy E, Shinobu LA, Galasko D, Thal LJ, Beal MF, Howell N, Parker WD, Jr. (1997) Mutations in mitochondrial cytochrome c oxidase

genes segregate with late-onset Alzheimer disease. *Proc Natl Acad Sci U S A* **94**, 4526-4531.

[103] Humphries KM, Szweda LI (1998) Selective inactivation of alpha-ketoglutarate dehydrogenase and pyruvate dehydrogenase: reaction of lipoic acid with 4-hydroxy-2-nonenal. *Biochemistry* **37**, 15835-15841.

[104] Floyd RA, Hensley K (2002) Oxidative stress in brain aging. Implications for therapeutics of neurodegenerative diseases. *Neurobiol Aging* **23**, 795-807.

[105] Busciglio J, Pelsman A, Wong C, Pigino G, Yuan M, Mori H, Yankner BA (2002) Altered metabolism of the amyloid beta precursor protein is associated with mitochondrial dysfunction in Down's syndrome. *Neuron* **33**, 677-688.

[106] Yao J, Taylor M, Davey F, Ren Y, Aiton J, Coote P, Fang F, Chen JX, Yan SD, Gunn-Moore FJ (2007) Interaction of amyloid binding alcohol dehydrogenase/Abeta mediates up-regulation of peroxiredoxin II in the brains of Alzheimer's disease patients and a transgenic Alzheimer's disease mouse model. *Mol Cell Neurosci* **35**, 377-382.