Biochimica et Biophysica Acta 1837 (2014) 1069–1074

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbabio

Review

Mitochondrial import and degradation of amyloid-β peptide ☆

Catarina Moreira Pinho, Pedro Filipe Teixeira *, Elzbieta Glaser **

Department of Biochemistry and Biophysics, Stockholm University, Arrhenius Laboratories for Natural Sciences, SE-106 91 Stockholm, Sweden

ARTICLE INFO

Article history:
Received 10 December 2013
Received in revised form 31 January 2014
Accepted 10 February 2014
Available online 18 February 2014

Keywords:
Mitochondria
Amyloid-β peptide
MAM
Degradation
Presequence protease
PreP

ABSTRACT

Mitochondrial dysfunctions associated with amyloid-β peptide (Aβ) accumulation in mitochondria have been observed in Alzheimer's disease (AD) patients' brains and in AD mice models. Aβ is produced by sequential action of β- and γ-secretases cleaving the amyloid precursor protein (APP). The γ-secretase complex was found in mitochondria-associated endoplasmic reticulum membranes (MAM) suggesting that this could be a potential site of Aβ production, from which Aβ is further transported into the mitochondria. In vitro, Aβ was shown to be imported into the mitochondria through the translocase of the outer membrane (TOM) complex. The mitochondrial presequence protease (PreP) is responsible for Aβ degradation reducing toxic effects of Aβ on mitochondrial functions. The proteolytic activity of PreP is, however, lower in AD brain temporal lobe mitochondria and in AD transgenic mice models, possibly due to an increased reactive oxygen species (ROS) production. Here, we review the intracellular mechanisms of Aβ production, its mitochondrial import and the intra-mitochondrial degradation. We also discuss the implications of a reduced efficiency of mitochondrial Aβ clearance for AD. Understanding the underlying mechanisms may provide new insights into mitochondria related pathogenesis of AD and development of drug therapy against AD. This article is part of a Special Issue entitled: 18th European Bioenergetic Conference.

1. Introduction

Alzheimer's disease (AD) is one of the most common and devastating age-related neurodegenerative disorders [1]. From the histopathological point of view, the brain of AD patients displays two major molecular hallmarks: the intracellular fibrillar tangles composed of hyperphosphorylated Tau and the extracellular neuritic plaques, mainly constituted by amyloid-β peptide (Aβ) [2]. In this review we will focus on the Aβ associated cellular interactions.

1.1. The life cycle of amyloid-β

Aβ is derived from the amyloid precursor protein (APP) by sequential proteolytic maturation steps catalyzed by the β- and γ-secretases. APP is a type I membrane protein containing a large extracellular N-terminal domain and the C-terminus positioned towards the intracellular space [3]. While the precise functions of APP are still unknown, different studies have indicated that APP and its proteolytic products could be involved in processes as diverse as axonal transport, transcriptional control, cell adhesion and apoptosis [4–8].

APP can be processed by different proteases either through a non-amyloidogenic pathway, that prevents the Aβ production, or by an amyloidogenic pathway, leading to Aβ production. The amyloidogenic pathway starts with an initial cleavage of APP by the β-secretase/BACE1 (β-site APP cleaving enzyme-1), giving rise to the soluble APPsβ and the β-C-terminal fragment (β-CTF). Subsequently, the β-CTF is cleaved by the γ-secretase complex (with the presenilins 1 and 2 (PS1/2), constituting the catalytic core of the complex) at the membrane level to generate Aβ [3]. The γ-cleavage can occur under physiological conditions between amino acids 37 and 43 of the Aβ sequence generating diverse Aβ species. Aβ1–40 is the most abundant species, but Aβ1–42 is the most toxic due to a higher hydrophobicity and therefore higher tendency for aggregation [9].

Throughout the years several hypotheses arose to explain AD pathology. Among these, the "amyloid hypothesis" and the "mitochondrial cascade hypothesis" have endured the test of time and are currently well accepted and documented [10–13]. The "amyloid hypothesis" postulates that the accumulation of Aβ in the brain is the primary cause influencing AD pathogenesis and, therefore, factors such as the incorrect processing of APP, increased Aβ synthesis and inefficient clearance are of capital importance for disease progression. The amyloid hypothesis is supported by the cases of familiar AD, FAD (around 1% of the AD cases) where mutations in genes such as *APP* (10–15% of FAD cases), *PSEN-1* (18–50% of FAD cases) and *PSEN-2* (rarely associated with FAD) (coding for PS1/2) lead to higher Aβ production and result in early onset AD [14,15]. The "mitochondrial cascade hypothesis" proposes that genetic factors (both in the nuclear and mitochondrial DNA) determine the efficiency of the mitochondrial electron transport chain and also the rate of production of reactive oxygen species. A

☆ This article is part of a Special Issue entitled: 18th European Bioenergetic Conference.

* Corresponding author. Tel.: +46 8 162472.
** Corresponding author. Tel.: +46 8 162457.
E-mail addresses: pedro@dbb.su.se (P.F. Teixeira), e_glaser@dbb.su.se (E. Glaser).

http://dx.doi.org/10.1016/j.bbabio.2014.02.007
0005-2728/

decline in the efficiency of mitochondrial activities (due to aging) with concomitant increase in the concentration of ROS then triggers the production of Aβ [11–13]. This hypothesis is especially useful to explain the occurrence of sporadic, late-onset AD. Even though these two hypotheses postulate different underlying causes, both converge in predicting an exacerbated Aβ production and its intracellular accumulation. Thus, it is currently accepted that an increase in the levels of Aβ (particularly Aβ1–42) over the years or even decades is correlated with AD progression, both in familiar and sporadic cases. Considering that Aβ is a natural product of metabolism and is present even in healthy cells, its cellular concentration must be kept within a precise range and therefore the balance between synthesis and degradation has to be carefully controlled. In terms of synthesis, currently it is not completely understood how the aberrant APP processing is triggered and precisely what factors affect Aβ distribution in the cell [10,16]. However, it has been shown that Aβ can be localized in different cellular compartments besides plasma membrane, namely in the endoplasmic reticulum (ER), mitochondria, endosomes, nucleus and in Golgi [17]. To balance the Aβ production, a range of different cellular proteases, localized in different compartments, such as neprilysin, insulin degrading enzyme, cathepsin and human presequence protease (hPreP) [18,19], has been shown to play an important role in the clearance of this peptide from the cell. Interestingly, few of these proteases were found either at lower level or with lowered activity in AD (see Section Reduced hPreP activity in AD brain mitochondria and AD transgenic mice models). This fact suggests that an impaired Aβ-clearance system will further lead to higher Aβ accumulation in AD [20–22].

1.2. Mitochondrial dysfunction in Alzheimer's disease

While it is well documented that AD is a multifactorial disease where many cellular components play a role, it has recently been recognized that mitochondrial dysfunction is among the earlier observed pathogenic alterations, detected well before the accumulation of neuritic plaques [23,24]. A growing number of studies are emerging reporting impaired mitochondrial functions including electron transfer, ATP synthesis, mitochondrial transcription, translation and protein synthesis, upregulation of voltage-dependent anion channel (VDAC), as well as increased production of reactive oxygen species (ROS) in AD patients and in AD transgenic mouse models [24–31]. Mitochondria are dynamic organelles undergoing frequent fusion and fission [32,33]. Interestingly, in AD an impaired balance between these two mechanisms was detected. Overexpression of APP_{wt} and APP_{Swe} in M17 cells resulted in lower levels of proteins associated with fusion (dynamin-related protein 1 (Drp1), optic atrophy 1 (OPA1), mitofusins-1 and -2 (Mfn1 and Mfn2)) and higher levels of fission 1 (Fis1), a protein involved in fission. The cells overexpressing APP_{wt} and APP_{Swe} exhibited fragmented mitochondria and perinuclear mitochondrial distribution [34,35]. Manczak and colleagues found that monomeric and oligomeric Aβs could interact with Drp1 in AD patients [36]. Interestingly, a mouse model of FAD (expressing mutant human presenilin 1, PS1M146L), showed impaired mitochondrial dynamics and aberrant morphology. These dysfunctions could be observed even before the formation of Aβ deposits and loss of memory [37].

The Aβ accumulation in mitochondria from postmortem AD brains, cellular and transgenic mice models has been well documented, providing evidence that Aβ is physically localized in mitochondria and is available for interaction with mitochondrial protein targets. In addition to Drp1, other characterized mitochondrial Aβ interactors are Aβ-binding alcohol dehydrogenase (ABAD), cyclophilin D (CypD), cytochrome c oxidase, VDAC and hPreP [31,38–47]. The functional consequences of these interactions are summarized in Table 1 and the implications for the progression of AD have been extensively reviewed elsewhere [25].

The connection between mitochondrial dysfunction and the progression of AD is currently not fully understood. On one hand mitochondrial dysfunction arises as a consequence of Aβ accumulation and through its interaction with intra-mitochondrial targets as overexpression of Aβ showed impairment of mitochondrial respiration, changed morphology and mobility of mitochondria [27,36,48–50]. On the other hand mitochondrial perturbations can itself act as trigger to modulate Aβ production and therefore induce imbalanced Aβ levels. In cell models it was shown that inhibition of mitochondrial complex I and complex III with rotenone and antimycin resulted in ROS-dependent elevated levels of Aβ [51]. Moreover, several other reports showed that inhibition of ATP production induced higher levels of BACE-1 and that elevated ROS induced Aβ production [52–57]. Therefore, it is likely that the pathogenic mitochondrial alterations in AD are a consequence of a cumulative effect where mitochondrial dysfunction and Aβ accumulation influence each other in a deadly vicious cycle.

Considering the central role of mitochondria for AD pathogenesis it is not surprising that this area has been a subject of intensive research. In the present review we focus on two aspects that are currently underrepresented in the literature: the mechanisms of import of Aβ into the mitochondria and the intra-mitochondrial degradation of this peptide by hPreP. Additionally, we also discuss the implications of a reduced efficiency of mitochondrial Aβ clearance for AD.

2. Aβ import into mitochondria

One of the essential points to clarify the effect of Aβ on mitochondrial physiology is to understand how Aβ reaches mitochondria, allowing the physical interaction with protein targets. Such a process would require Aβ to be produced either within the mitochondria or in the close vicinity.

APP has an ER signal peptide followed by a cryptic mitochondrial targeting signal, and an internal domain enriched in acidic amino acids. It has been shown that the acidic domain in APP can form stable complexes with the translocase of the outer mitochondrial membrane (TOM) and the translocase of the inner mitochondrial membrane (TIM), which causes it to accumulate in the mitochondrial translocation system [58,59]. It has been proposed that the C-terminal transmembrane sequence of APP becomes inserted into the mitochondrial outer membrane. Further, APP accumulated within translocation channels is cleaved by Omi protease located in the mitochondrial inter membrane space (IMS), whereas the APP C-terminal part outside of mitochondria is cleaved by α/β-secretases. That would generate an APP fragment

Table 1
Mitochondrial Aβ interactors and the effects of their interaction with Aβ.

Mitochondrial target	Effect of Aβ	Reference(s)
ABAD	Blocking of the NADH binding site, ROS production	[42–45]
Cyclophilin D	Opening of the mitochondrial permeability transition pore	[39,40]
ATP synthase	Binding to $F_1\alpha$ of ATP synthase. Inhibition of ATP synthase	[31]
hPreP	Substrate for degradation	[38,41]
Cytochrome c oxidase	Binding to subunit 1 impairing protein activity and respiration	[46]
VDAC	Blocking of the mitochondrial pores, interrupting metabolite transport	[47]
Drp1	Mitochondrial fragmentation, disruption of mitochondrial dynamics	[36]

immobilized in the outer membrane that would be further processed by γ-secretase, found to partially localize in mitochondria, resulting in the production of Aβ peptides in the IMS [58]. However, the intra-mitochondrial Aβ production remains to be experimentally proven. Another possibility is that Aβ could be transported from the outside of the cell through endocytosis and vesicular transport and released close to the mitochondria. Indeed, it has been shown that extracellular Aβ can be taken up by neuroblastoma cells and localized to the mitochondria [60]. Moreover, it has been demonstrated that the receptor for advanced glycation end products (RAGE) is involved in the transport of Aβ from the cell surface to the intracellular space [61]. Alternatively, it has been proposed that Aβ can be directly translocated from MAM to the mitochondria through the contact points between these organelles [62], which will be described and discussed below.

2.1. MAM as a possible route for Aβ entry to mitochondria

Mitochondria-associated endoplasmic reticulum membranes (MAM) are a physical connection between the ER membrane and the mitochondrial outer membrane and play essential roles in lipid synthesis and transport between the two organelles, fatty acids, glucose and cholesterol metabolism, Ca^{2+} homeostasis and apoptosis (reviewed elsewhere [63,64]). Accordingly, proteins such as phosphatidylserine synthase-1 and -2 (PSS-1, PSS-2), long-chain fatty acid-CoA ligase type 4 (FACL-4), Sigma1R, inositol 1,4,5-triphosphate receptor (IP3R) and phosphofurin acidic cluster sorting protein-2 (PACS-2) were found in MAM (Fig. 1A). The tethering between the two organelles is mainly done through mitofusin-2 (Mfn-2) and the cytosolic chaperone Grp75, which binds to the IP3R (ER side) and to VDAC-1 (mitochondria side) [65,66].

MAM have recently attracted considerable interest in connection with AD research. In a recent study from our laboratory, we showed that MAM are present in neuronal cells. When two MAM components, Sigma1R and PACS-2, were knocked down by siRNA in primary hippocampal neurons the result was cell degeneration coinciding with activation of caspase-3, supporting the idea that MAM are essential for neuronal cell survival [67]. An altered expression of MAM-associated proteins (PSS-1, PACS-2 and Sigma1R) in postmortem AD brains and AD transgenic mice models was also shown [67]. Furthermore, PS-knockout cells, PS-knockdown cells and fibroblasts from familial AD and sporadic AD patients showed increased MAM functions and a higher area of ER-mitochondria apposition [68]. Accordingly, SH-SY5Y cells exposed to Aβ presented elevated MAM contact points leading to enhanced Ca^{2+} transport between the organelles [67]. The altered MAM functions in AD have been reviewed in more detail elsewhere [68]. Interestingly, Area-Gomez et al. showed that PS1 and PS2 were enriched in MAM and that the γ-secretase complex was active in this

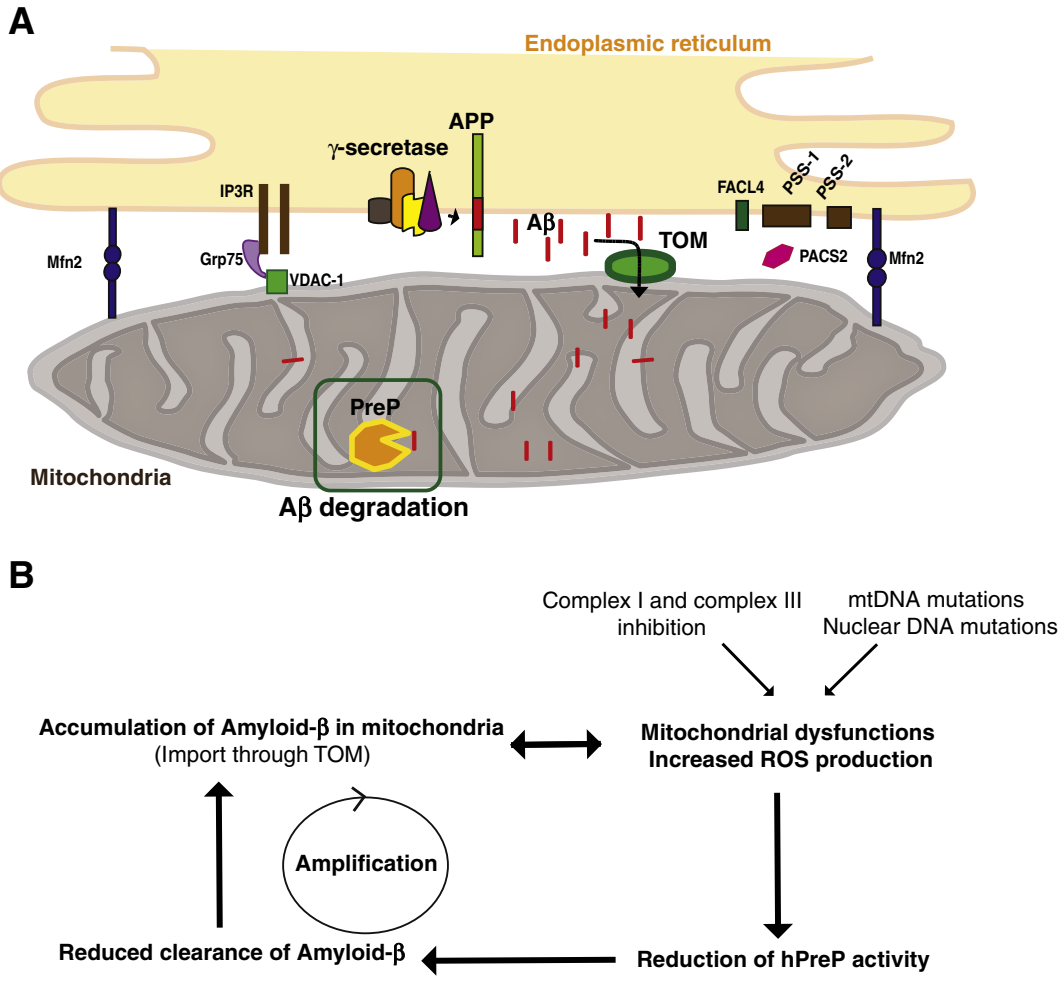

Fig. 1. A. Model of the Aβ synthesis in mitochondria-associated endoplasmic reticulum membranes (MAM) and further mitochondrial import of the Aβ peptide. MAM are a physical interaction between ER membrane and mitochondrial outer membrane with mitofusin-2 (Mfn2) being important for the membrane tethering. MAM contain proteins involved in different mechanisms such as phospholipid metabolism (e.g. PSS-1/-2 and FACL4), Ca^{2+} transport between the two organelles (e.g. IP3R, VDAC-1 and Grp75) and apoptosis (e.g. PACS-2). Active γ-secretase complex (PS-1/-2, nicastrin, APH1 and PS) is present in MAM, potentially giving rise to Aβ in the vicinity of mitochondria. Aβ can further be imported into mitochondria through the TOM complex, and be degraded by the matrix-localized hPreP to avoid toxic effects of Aβ on the mitochondrial functions. B. ROS-dependent inactivation of PreP leading to amplification of Aβ accumulation in mitochondria.

area [62]. Also, MAM exhibit lipid raft characteristics, which constitute a favorable environment for γ-secretase activity against APP [69,70]. Taken together, these observations highlight MAM as a possible site of Aβ production in close proximity to the mitochondria, suggesting this pathway as a possible source of mitochondria-localized Aβ [62].

2.2. Import of Aβ through the translocase of the outer mitochondrial membrane (TOM) complex

Most mitochondrial proteins are synthesized in cytosolic ribosomes and post-translationally imported into the different organellar sub-compartments. The precursor proteins destined to the mitochondrial matrix are synthesized with an N-terminal extension (the presequence) that is recognized by dedicated receptors in the mitochondrial outer membrane. Following the recognition event, the pre-proteins are translocated through the mitochondrial entry gate, the TOM complex and then via TIM to the matrix (reviewed by [71]). Studies from our laboratory showed that Aβ1–40 and Aβ1–42 can be imported in vitro into the mitochondria through the TOM complex in a similar fashion as a typical mitochondrial localized protein (e.g. $F_1\beta$ subunit of ATP synthase). Antibodies directed towards the Tom20, Tom40 and Tom70 components of the TOM complex inhibited Aβ import. Notably, the uptake of Aβ was not affected by antibodies against the VDAC nor by cyclosporine A, which is an inhibitor of the mitochondrial permeability transition pore (PTP). Even though the Aβ sequence does not resemble a classical presequence peptide, it is possible that the helical structure, which Aβ adopts in the membrane environment (reviewed by [72]), is sufficient for recognition by the TOM complex. However, in contrast to the import of matrix proteins, when valinomycin (an ionophore that disrupts the membrane potential, $\Delta\Psi$) was applied, the peptides could still be imported, revealing that Aβ import is independent of $\Delta\Psi$. The imported Aβ was mostly present in the cristae and in the isolated inner membrane fractions, but also in the matrix [60]. Considering there are several pathways for translocation (TIM23) and insertion (TIM23/TIM22) of proteins into the inner mitochondrial membrane it is currently not known in mechanistic details how Aβ gains access to the different mitochondrial sub-compartments.

3. Aβ degradation in mitochondria

3.1. Presequence protease (PreP)

To ensure a correct sorting and targeting most of the mitochondrial proteins contain a targeting sequence, designated presequence. This presequence is used for recognition by the translocation machinery and is removed by the mitochondrial processing peptidase (MPP) when the protein reaches its correct destination. The free presequence peptides have amphipathic characteristics and have been shown to affect mitochondrial membrane integrity, uncouple oxidative phosphorylation and inhibit enzyme activity (e.g. MPP) (reviewed by [73]). Presequence protease (PreP), localized in the mitochondrial matrix, is responsible for the degradation of the presequences completing the last step of the protein import process [41,74].

PreP was initially identified in *Arabidopsis thaliana*, and shown to degrade targeting peptides of both mitochondria and chloroplasts [74,75]. In addition to targeting peptides generated by processing, PreP degrades a wide range of unstructured peptides ranging from 10 to 65 a.a. The crystal structure of AtPreP1 revealed a large catalytic chamber of 10,000 $Å^3$, big enough to accommodate unstructured peptides up to 65 a.a long, but precluding the degradation of larger folded proteins [76].

Human PreP was initially identified as metalloprotease 1 [77], and shows 31% sequence identity to AtPreP performing a similar function in the degradation of presequences and other unstructured peptides. Notably, hPreP can also degrade Aβ. Through immunoinactivation assays with isolated mitochondria, it was found that hPreP is the only protease in the mitochondria responsible for the degradation of Aβ [41]. In vitro, hPreP can degrade Aβ1–40, Aβ1–42 and the Aβ arctic (Aβ1–40 E22G), a peptide that causes increased fibril formation and early onset of a familial variant of AD. Analysis of the hPreP cleavage sites on the Aβ by mass spectrometry showed the generation of several fragments, which were unique for hPreP (in comparison to other proteases), including the cleavage sites in the very hydrophobic C-terminal portion of Aβ that is prone to aggregation. There was a mild preference for hydrophobic and small uncharged amino acids at both the P_1 and P'_1 positions [41]. Even though the Aβ peptides differ from presequences in terms of both amino acid composition and physicochemical properties, the lack of strict sequence specificity for cleavage enables hPreP to degrade a wide range of substrates [74,75].

3.2. Reduced hPreP activity in AD brain mitochondria and AD transgenic mice models

Considering that hPreP can degrade mitochondria-localized Aβ peptides, this protease is clearly an important regulator of Aβ concentration within the mitochondria and therefore perturbation of hPreP activity can potentially influence Aβ accumulation [41]. In collaboration with Yan laboratory, we have analyzed the activity of hPreP in mitochondrial matrix fractions isolated from the brain temporal lobe (an area of brain highly susceptible to Aβ accumulation) of AD patients and age-matched controls using three different substrates (Aβ1–40, Aβ1–42 and the $F_1\beta$ presequence). The results showed a significantly lower hPreP activity in AD temporal lobe compared to the control samples. Interestingly, when the activity was measured in mitochondria isolated from the cerebellum (an area not affected in AD) no differences in hPreP activity between AD brains and controls were observed. Similar experiments performed using mitochondria from brains of AD transgenic mice models overexpressing APP or APP and ABAD (ABAD overexpression further exacerbates the mitochondrial dysfunction observed in AD models) showed again lower hPreP activity compared to the aged-matched non-transgenic mice. Furthermore, the proteolytic activity of hPreP decreased in an age dependent manner showing lower activity in twelve-month-old transgenic mice compared to five-month old mice [38]. These results are of great importance considering that, from the functional point of view, a reduction of hPreP activity in AD brain mitochondria has consequences for the accumulation not only of Aβ but also, potentially, of free presequence peptides that have themselves toxic effects on mitochondria [73]. The potential toxic effect caused by presequence peptide accumulation in the mitochondria when hPreP activity is reduced might contribute to exacerbate mitochondrial dysfunction but the specific relevance of this accumulation remains to be determined.

In a gene-wide association study, 18 single nucleotide polymorphisms (SNPs) present in *PITRM1* (gene encoding hPreP) were genotyped in 673 AD cases and 649 controls in a Swedish population but no correlation between these mutations and AD progression could be identified. However, a functional analysis of several hPreP-SNP variants, selected on the basis of localization of the substituted amino acid in the enzyme structure, showed a decreased activity in comparison to wild type hPreP [78].

3.3. Exposure to ROS inhibits hPreP activity

It is noteworthy that the lower hPreP activity in AD brain mitochondria was not due to lowered protein levels, suggesting that this reduction is likely due to a functional alteration of the enzyme, for instance through post-translational modifications such as protein oxidation [38]. Oxidative stress is a well-documented alteration observed in AD brains and the increase in several ROS markers has been reported [79,80]. The levels of 4-hydroxynonenal, a by-product of lipid peroxidation and a biomarker of oxidation, were found to be higher in the temporal lobe of AD patients, in comparison to controls, but the levels were

unchanged in the cerebellum [38]. These results suggest that one possibility to explain the lower hPreP activity in the temporal lobe is protein oxidation. Several biochemical analyses using purified hPreP support this idea. hPreP activity was shown to be inhibited by exposure to H_2O_2 in a concentration-dependent manner [81]. Even though the mechanism is not completely clear, it has been shown that hPreP inactivation involved the formation of disulfide bridges that could potentially lock the enzyme in an inactive conformation [41]. Additionally, we were also able to show that the lower hPreP activity could be reverted by methionine sulfoxide reductase A (MsrA) although further studies are necessary to clarify the exact role of MsrA in the recovery process [81]. Additional evidence for the correlation between the accumulation of ROS and reduced hPreP activity came from experiments performed in a mouse model of AD overexpressing both APP and ABAD. In such model, the formation of an ABAD–Aβ complex in the mitochondria reduces ABAD activity leading to an increased ROS production and exacerbating mitochondrial dysfunction [44]. Interestingly, the introduction of a decoy peptide that prevents ABAD–Aβ interaction into the ABAD overexpressor mice results in the reduction of ROS levels and increase in hPreP activity with a concomitant reduction in Aβ levels [45].

4. Concluding remarks

It is becoming increasingly clear that alterations in mitochondrial function, morphology and dynamics associated with Aβ accumulation and/or ROS production are among the earliest observed pathogenic alterations observed in AD, preceding the formation of amyloid plaques [23,24]. It can be hypothesized that the accumulation of Aβ observed at early stages of AD would lead to altered MAM activities, increased Aβ import and ROS production in the mitochondria, as supported by studies with transgenic AD mice models [20,21]. Elevated levels of ROS will affect PreP lowering its activity consequently resulting in the accumulation in the mitochondria of potentially toxic presequence peptides as well as Aβ (Fig. 1B). Accumulation of Aβ will allow subsequent interactions with different mitochondrial interactors (cf. Table 1) leading to increased mitochondrial toxicity and neuronal death that is exacerbated in AD. Therefore, it is important to understand the life cycle of Aβ in mitochondria, from the mechanisms underlying its mitochondrial import and localization to its proteolytic degradation, as these pathways may present new targets for therapeutic intervention. From the current knowledge, one could envisage the usefulness of drugs that would either specifically affect the MAM region or would inhibit Aβ import through the TOM complex or that would activate hPreP favoring Aβ degradation, either way reducing the local concentration of Aβ. In this context, several questions still remain open, particularly how Aβ gains access to the mitochondrial entry gate (e.g. through localized synthesis in the MAM region or possibly through endocytosis and vesicular transport) and the mechanism for regulation of hPreP activity by ROS.

Acknowledgements

This work was supported by research grants from the Swedish Research Council and the Swedish Alzheimer Foundation to EG.

References

[1] L. Mucke, Neuroscience: Alzheimer's disease, Nature 461 (2009) 895–897.
[2] R.J. Castellani, R.K. Rolston, M.A. Smith, Alzheimer disease, Dis. Mon. 56 (2010) 484–546.
[3] R.J. O'Brien, P.C. Wong, Amyloid precursor protein processing and Alzheimer's disease, Annu. Rev. Neurosci. 34 (2011) 185–204.
[4] U. Konietzko, Z.V. Goodger, M. Meyer, B.M. Kohli, J. Bosset, D.K. Lahiri, R.M. Nitsch, Co-localization of the amyloid precursor protein and Notch intracellular domains in nuclear transcription factories, Neurobiol. Aging 31 (2010) 58–73.
[5] H. Meziane, J.C. Dodart, C. Mathis, S. Little, J. Clemens, S.M. Paul, A. Ungerer, Memory-enhancing effects of secreted forms of the beta-amyloid precursor protein in normal and amnestic mice, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 12683–12688.
[6] A. Nikolaev, T. McLaughlin, D.D. O'Leary, M. Tessier-Lavigne, APP binds DR6 to trigger axon pruning and neuron death via distinct caspases, Nature 457 (2009) 981–989.
[7] J.M. Roch, E. Masliah, A.C. Roch-Levecq, M.P. Sundsmo, D.A. Otero, I. Veinbergs, T. Saitoh, Increase of synaptic density and memory retention by a peptide representing the trophic domain of the amyloid beta/A4 protein precursor, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 7450–7454.
[8] T.L. Young-Pearse, J. Bai, R. Chang, J.B. Zheng, J.J. LoTurco, D.J. Selkoe, A critical function for beta-amyloid precursor protein in neuronal migration revealed by in utero RNA interference, J. Neurosci. 27 (2007) 14459–14469.
[9] C. Haass, D.J. Selkoe, Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide, Nat. Rev. Mol. Cell Biol. 8 (2007) 101–112.
[10] J. Hardy, D.J. Selkoe, The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics, Science (New York, N.Y.) 297 (2002) 353–356.
[11] R.H. Swerdlow, J.M. Burns, S.M. Khan, The Alzheimer's disease mitochondrial cascade hypothesis, J. Alzheimers Dis. 20 (Suppl. 2) (2010) S265–S279.
[12] R.H. Swerdlow, J.M. Burns, S.M. Khan, The Alzheimer's disease mitochondrial cascade hypothesis: progress and perspectives, Biochim. Biophys. Acta (2013) (in press, http://dx.doi.org/10.1016/j.bbadis.2013.09.010).
[13] R.H. Swerdlow, S.M. Khan, A "mitochondrial cascade hypothesis" for sporadic Alzheimer's disease, Med. Hypotheses 63 (2004) 8–20.
[14] L.M. Bekris, C.E. Yu, T.D. Bird, D.W. Tsuang, Genetics of Alzheimer disease, J. Geriatr. Psychiatry Neurol. 23 (2010) 213–227.
[15] J. Theuns, J. Del-Favero, B. Dermaut, C.M. van Duijn, H. Backhovens, M.V. Van den Broeck, S. Serneels, E. Corsmit, C.V. Van Broeckhoven, M. Cruts, Genetic variability in the regulatory region of presenilin 1 associated with risk for Alzheimer's disease and variable expression, Hum. Mol. Genet. 9 (2000) 325–331.
[16] H.W. Querfurth, F.M. LaFerla, Alzheimer's disease, N. Engl. J. Med. 362 (2010) 329–344.
[17] B. Penke, A.M. Toth, I. Foldi, M. Szucs, T. Janaky, Intraneuronal beta-amyloid and its interactions with proteins and subcellular organelles, Electrophoresis 33 (2012) 3608–3616.
[18] M.A. Leissring, The AbetaCs of Abeta-cleaving proteases, J. Biol. Chem. 283 (2008) 29645–29649.
[19] N.N. Nalivaeva, L.R. Fisk, N.D. Belyaev, A.J. Turner, Amyloid-degrading enzymes as therapeutic targets in Alzheimer's disease, Curr. Alzheimer Res. 5 (2008) 212–224.
[20] A. Caccamo, S. Oddo, M.C. Sugarman, Y. Akbari, F.M. LaFerla, Age- and region-dependent alterations in Abeta-degrading enzymes: implications for Abeta-induced disorders, Neurobiol. Aging 26 (2005) 645–654.
[21] M. Kim, L.B. Hersh, M.A. Leissring, M. Ingelsson, T. Matsui, W. Farris, A. Lu, B.T. Hyman, D.J. Selkoe, L. Bertram, R.E. Tanzi, Decreased catalytic activity of the insulin-degrading enzyme in chromosome 10-linked Alzheimer disease families, J. Biol. Chem. 282 (2007) 7825–7832.
[22] Z. Zhao, Z. Xiang, V. Haroutunian, J.D. Buxbaum, B. Stetka, G.M. Pasinetti, Insulin degrading enzyme activity selectively decreases in the hippocampal formation of cases at high risk to develop Alzheimer's disease, Neurobiol. Aging 28 (2007) 824–830.
[23] V. Rhein, X. Song, A. Wiesner, L.M. Ittner, G. Baysang, F. Meier, L. Ozmen, H. Bluethmann, S. Drose, U. Brandt, E. Savaskan, C. Czech, J. Gotz, A. Eckert, Amyloid-beta and tau synergistically impair the oxidative phosphorylation system in triple transgenic Alzheimer's disease mice, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 20057–20062.
[24] J. Yao, R.W. Irwin, L. Zhao, J. Nilsen, R.T. Hamilton, R.D. Brinton, Mitochondrial bioenergetic deficit precedes Alzheimer's pathology in female mouse model of Alzheimer's disease, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 14670–14675.
[25] P.J. Crouch, S.M. Harding, A.R. White, J. Camakaris, A.I. Bush, C.L. Masters, Mechanisms of A beta mediated neurodegeneration in Alzheimer's disease, Int. J. Biochem. Cell Biol. 40 (2008) 181–198.
[26] A.M. Aleardi, G. Benard, O. Augereau, M. Malgat, J.C. Talbot, J.P. Mazat, T. Letellier, J. Dachary-Prigent, G.C. Solaini, R. Rossignol, Gradual alteration of mitochondrial structure and function by beta-amyloids: importance of membrane viscosity changes, energy deprivation, reactive oxygen species production, and cytochrome c release, J. Bioenerg. Biomembr. 37 (2005) 207–225.
[27] M.J. Calkins, M. Manczak, P. Mao, U. Shirendeb, P.H. Reddy, Impaired mitochondrial biogenesis, defective axonal transport of mitochondria, abnormal mitochondrial dynamics and synaptic degeneration in a mouse model of Alzheimer's disease, Hum. Mol. Genet. 20 (2011) 4515–4529.
[28] C.S. Casley, L. Canevari, J.M. Land, J.B. Clark, M.A. Sharpe, Beta-amyloid inhibits integrated mitochondrial respiration and key enzyme activities, J. Neurochem. 80 (2002) 91–100.
[29] M. Manczak, P. Mao, M.J. Calkins, A. Cornea, A.P. Reddy, M.P. Murphy, H.H. Szeto, B. Park, P.H. Reddy, Mitochondria-targeted antioxidants protect against amyloid-beta toxicity in Alzheimer's disease neurons, J. Alzheimers Dis. 20 (Suppl. 2) (2010) S609–S631.
[30] K. Matsumoto, Y. Akao, H. Yi, M. Shamoto-Nagai, W. Maruyama, M. Naoi, Overexpression of amyloid precursor protein induces susceptibility to oxidative stress in human neuroblastoma SH-SY5Y cells, J. Neural Transm. 113 (2006) 125–135.
[31] C. Schmidt, E. Lepsverdize, S.L. Chi, A.M. Das, S.V. Pizzo, A. Dityatev, M. Schachner, Amyloid precursor protein and amyloid beta-peptide bind to ATP synthase and regulate its activity at the surface of neural cells, Mol. Psychiatry 13 (2008) 953–969.
[32] S.M. Rafelski, Mitochondrial network morphology: building an integrative, geometrical view, BMC Biol. 11 (2013) 71.
[33] A.M. van der Bliek, Q. Shen, S. Kawajiri, Mechanisms of mitochondrial fission and fusion, Cold Spring Harb. Perspect. Biol. 5 (2013).
[34] X. Wang, B. Su, H.G. Lee, X. Li, G. Perry, M.A. Smith, X. Zhu, Impaired balance of mitochondrial fission and fusion in Alzheimer's disease, J. Neurosci. 29 (2009) 9090–9103.

[35] X. Wang, B. Su, S.L. Siedlak, P.I. Moreira, H. Fujioka, Y. Wang, G. Casadesus, X. Zhu, Amyloid-beta overproduction causes abnormal mitochondrial dynamics via differential modulation of mitochondrial fission/fusion proteins, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 19318–19323.
[36] M. Manczak, M.J. Calkins, P.H. Reddy, Impaired mitochondrial dynamics and abnormal interaction of amyloid beta with mitochondrial protein Drp1 in neurons from patients with Alzheimer's disease: implications for neuronal damage, Hum. Mol. Genet. 20 (2011) 2495–2509.
[37] E. Trushina, E. Nemutlu, S. Zhang, T. Christensen, J. Camp, J. Mesa, A. Siddiqui, Y. Tamura, H. Sesaki, T.M. Wengenack, P.P. Dzeja, J.F. Poduslo, Defects in mitochondrial dynamics and metabolomic signatures of evolving energetic stress in mouse models of familial Alzheimer's disease, PLoS One 7 (2012) e32737.
[38] N. Alikhani, L. Guo, S. Yan, H. Du, C.M. Pinho, J.X. Chen, E. Glaser, S.S. Yan, Decreased proteolytic activity of the mitochondrial amyloid-beta degrading enzyme, PreP peptidasome, in Alzheimer's disease brain mitochondria, J. Alzheimers Dis. 27 (2011) 75–87.
[39] H. Du, L. Guo, F. Fang, D. Chen, A.A. Sosunov, G.M. McKhann, Y. Yan, C. Wang, H. Zhang, J.D. Molkentin, F.J. Gunn-Moore, J.P. Vonsattel, O. Arancio, J.X. Chen, S.D. Yan, Cyclophilin D deficiency attenuates mitochondrial and neuronal perturbation and ameliorates learning and memory in Alzheimer's disease, Nat. Med. 14 (2008) 1097–1105.
[40] H. Du, L. Guo, W. Zhang, M. Rydzewska, S. Yan, Cyclophilin D deficiency improves mitochondrial function and learning/memory in aging Alzheimer disease mouse model, Neurobiol. Aging 32 (2011) 398–406.
[41] A. Falkevall, N. Alikhani, S. Bhushan, P.F. Pavlov, K. Busch, K.A. Johnson, T. Eneqvist, L. Tjernberg, M. Ankarcrona, E. Glaser, Degradation of the amyloid beta-protein by the novel mitochondrial peptidasome, PreP, J. Biol. Chem. 281 (2006) 29096–29104.
[42] J.W. Lustbader, M. Cirilli, C. Lin, H.W. Xu, K. Takuma, N. Wang, C. Caspersen, X. Chen, S. Pollak, M. Chaney, F. Trinchese, S. Liu, F. Gunn-Moore, L.F. Lue, D.G. Walker, P. Kuppusamy, Z.L. Zewier, O. Arancio, D. Stern, S.S. Yan, H. Wu, ABAD directly links Abeta to mitochondrial toxicity in Alzheimer's disease, Science (New York, N.Y.) 304 (2004) 448–452.
[43] J.S. Seo, K.W. Lee, T.K. Kim, I.S. Baek, J.Y. Im, P.L. Han, Behavioral stress causes mitochondrial dysfunction via ABAD up-regulation and aggravates plaque pathology in the brain of a mouse model of Alzheimer disease, Free Radic. Biol. Med. 50 (2011) 1526–1535.
[44] K. Takuma, J. Yao, J. Huang, H. Xu, X. Chen, J. Luddy, A.C. Trillat, D.M. Stern, O. Arancio, S.S. Yan, ABAD enhances Abeta-induced cell stress via mitochondrial dysfunction, FASEB J. 19 (2005) 597–598.
[45] J. Yao, H. Du, S. Yan, F. Fang, C. Wang, L.F. Lue, L. Guo, D. Chen, D.M. Stern, F.J. Gunn Moore, J. Xi Chen, O. Arancio, S.S. Yan, Inhibition of amyloid-beta (Abeta) peptide-binding alcohol dehydrogenase-Abeta interaction reduces Abeta accumulation and improves mitochondrial function in a mouse model of Alzheimer's disease, J. Neurosci. 31 (2011) 2313–2320.
[46] L.F. Hernandez-Zimbron, J. Luna-Munoz, R. Mena, R. Vazquez-Ramirez, C. Kubli-Garfias, D.H. Cribbs, K. Manoutcharian, G. Gevorkian, Amyloid-beta peptide binds to cytochrome C oxidase subunit 1, PLoS One 7 (2012) e42344.
[47] M. Manczak, P.H. Reddy, Abnormal interaction of VDAC1 with amyloid beta and phosphorylated tau causes mitochondrial dysfunction in Alzheimer's disease, Hum. Mol. Genet. 21 (2012) 5131–5146.
[48] M.J. Calkins, P.H. Reddy, Amyloid beta impairs mitochondrial anterograde transport and degenerates synapses in Alzheimer's disease neurons, Biochim. Biophys. Acta 1812 (2011) 507–513.
[49] S.M. Cardoso, I. Santana, R.H. Swerdlow, C.R. Oliveira, Mitochondria dysfunction of Alzheimer's disease cybrids enhances Abeta toxicity, J. Neurochem. 89 (2004) 1417–1426.
[50] S.J. Kish, F. Mastrogiacomo, M. Guttman, Y. Furukawa, J.W. Taanman, S. Dozic, M. Pandolfo, J. Lamarche, L. DiStefano, L.J. Chang, Decreased brain protein levels of cytochrome oxidase subunits in Alzheimer's disease and in hereditary spinocerebellar ataxia disorders: a nonspecific change? J. Neurochem. 72 (1999) 700–707.
[51] K. Leuner, T. Schutt, C. Kurz, S.H. Eckert, C. Schiller, A. Occhipinti, S. Mai, M. Jendrach, G.P. Eckert, S.E. Kruse, R.D. Palmiter, U. Brandt, S. Drose, I. Wittig, M. Willem, C. Haass, A.S. Reichert, W.E. Muller, Mitochondrion-derived reactive oxygen species lead to enhanced amyloid beta formation, Antioxid. Redox Signal. 16 (2012) 1421–1433.
[52] J. Busciglio, A. Pelsman, C. Wong, G. Pigino, M. Yuan, H. Mori, B.A. Yankner, Altered metabolism of the amyloid beta precursor protein is associated with mitochondrial dysfunction in Down's syndrome, Neuron 33 (2002) 677–688.
[53] L. Esposito, J. Raber, L. Kekonius, F. Yan, G.Q. Yu, N. Bien-Ly, J. Puolivali, K. Scearce-Levie, E. Masliah, L. Mucke, Reduction in mitochondrial superoxide dismutase modulates Alzheimer's disease-like pathology and accelerates the onset of behavioral changes in human amyloid precursor protein transgenic mice, J. Neurosci. 26 (2006) 5167–5179.
[54] T. Ma, C.A. Hoeffer, H. Wong, C.A. Massaad, P. Zhou, C. Iadecola, M.P. Murphy, R.G. Pautler, E. Klann, Amyloid beta-induced impairments in hippocampal synaptic plasticity are rescued by decreasing mitochondrial superoxide, J. Neurosci. 31 (2011) 5589–5595.
[55] C.A. Massaad, T.M. Washington, R.G. Pautler, E. Klann, Overexpression of SOD-2 reduces hippocampal superoxide and prevents memory deficits in a mouse model of Alzheimer's disease, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 13576–13581.
[56] Y. Ohyagi, T. Yamada, K. Nishioka, N.J. Clarke, A.J. Tomlinson, S. Naylor, Y. Nakabeppu, J. Kira, S.G. Younkin, Selective increase in cellular A beta 42 is related to apoptosis but not necrosis, Neuroreport 11 (2000) 167–171.
[57] R.A. Velliquette, T. O'Connor, R. Vassar, Energy inhibition elevates beta-secretase levels and activity and is potentially amyloidogenic in APP transgenic mice: possible early events in Alzheimer's disease pathogenesis, J. Neurosci. 25 (2005) 10874–10883.
[58] H.K. Anandatheerthavarada, G. Biswas, M.A. Robin, N.G. Avadhani, Mitochondrial targeting and a novel transmembrane arrest of Alzheimer's amyloid precursor protein impairs mitochondrial function in neuronal cells, J. Cell Biol. 161 (2003) 41–54.
[59] P.F. Pavlov, B. Wiehager, J. Sakai, S. Frykman, H. Behbahani, B. Winblad, M. Ankarcrona, Mitochondrial gamma-secretase participates in the metabolism of mitochondria-associated amyloid precursor protein, FASEB J. 25 (2011) 78–88.
[60] C.A. Hansson Petersen, N. Alikhani, H. Behbahani, B. Wiehager, P.F. Pavlov, I. Alafuzoff, V. Leinonen, A. Ito, B. Winblad, E. Glaser, M. Ankarcrona, 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 (2008) 13145–13150.
[61] K. Takuma, F. Fang, W. Zhang, S. Yan, E. Fukuzaki, H. Du, A. Sosunov, G. McKhann, Y. Funatsu, N. Nakamichi, T. Nagai, H. Mizoguchi, D. Ibi, O. Hori, S. Ogawa, D.M. Stern, K. Yamada, S.S. Yan, RAGE-mediated signaling contributes to intraneuronal transport of amyloid-beta and neuronal dysfunction, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 20021–20026.
[62] E. Area-Gomez, A.J. de Groof, I. Boldogh, T.D. Bird, G.E. Gibson, C.M. Koehler, W.H. Yu, K.E. Duff, M.P. Yaffe, L.A. Pon, E.A. Schon, Presenilins are enriched in endoplasmic reticulum membranes associated with mitochondria, Am. J. Pathol. 175 (2009) 1810–1816.
[63] O.M. de Brito, L. Scorrano, An intimate liaison: spatial organization of the endoplasmic reticulum–mitochondria relationship, EMBO J. 29 (2010) 2715–2723.
[64] T. Hayashi, R. Rizzuto, G. Hajnoczky, T.P. Su, MAM: more than just a housekeeper, Trends Cell Biol. 19 (2009) 81–88.
[65] O.M. de Brito, L. Scorrano, Mitofusin 2 tethers endoplasmic reticulum to mitochondria, Nature 456 (2008) 605–610.
[66] G. Csordas, C. Renken, P. Varnai, L. Walter, D. Weaver, K.F. Buttle, T. Balla, C.A. Mannella, G. Hajnoczky, Structural and functional features and significance of the physical linkage between ER and mitochondria, J. Cell Biol. 174 (2006) 915–921.
[67] L. Hedskog, C.M. Pinho, R. Filadi, A. Ronnback, L. Hertwig, B. Wiehager, P. Larssen, S. Gellhaar, A. Sandebring, M. Westerlund, C. Graff, B. Winblad, D. Galter, H. Behbahani, P. Pizzo, E. Glaser, M. Ankarcrona, Modulation of the endoplasmic reticulum–mitochondria interface in Alzheimer's disease and related models, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 7916–7921.
[68] E. Area-Gomez, M. Del Carmen Lara Castillo, M.D. Tambini, C. Guardia-Laguarta, A.J. de Groof, M. Madra, J. Ikenouchi, M. Umeda, T.D. Bird, S.L. Sturley, E.A. Schon, Upregulated function of mitochondria-associated ER membranes in Alzheimer disease, EMBO J. 31 (2012) 4106–4123.
[69] K.A. McMahon, M. Zhu, S.W. Kwon, P. Liu, Y. Zhao, R.G. Anderson, Detergent-free caveolae proteome suggests an interaction with ER and mitochondria, Proteomics 6 (2006) 143–152.
[70] T. Hayashi, M. Fujimoto, Detergent-resistant microdomains determine the localization of sigma-1 receptors to the endoplasmic reticulum–mitochondria junction, Mol. Pharmacol. 77 (2010) 517–528.
[71] N. Bolender, A. Sickmann, R. Wagner, C. Meisinger, N. Pfanner, Multiple pathways for sorting mitochondrial precursor proteins, EMBO Rep. 9 (2008) 42–49.
[72] L.C. Serpell, Alzheimer's amyloid fibrils: structure and assembly, Biochim. Biophys. Acta 1502 (2000) 16–30.
[73] P.F. Teixeira, E. Glaser, Processing peptidases in mitochondria and chloroplasts, Biochim. Biophys. Acta 1833 (2013) 360–370.
[74] A. Stahl, S. Nilsson, P. Lundberg, S. Bhushan, H. Biverstahl, P. Moberg, M. Morisset, A. Vener, L. Maler, U. Langel, E. Glaser, Two novel targeting peptide degrading proteases, PrePs, in mitochondria and chloroplasts, so similar and still different, J. Mol. Biol. 349 (2005) 847–860.
[75] B. Kmiec, P.F. Teixeira, R.P. Berntsson, M.W. Murcha, R.M. Branca, J.D. Radomiljac, J. Regberg, L.M. Svensson, A. Bakali, U. Langel, J. Lehtio, J. Whelan, P. Stenmark, E. Glaser, Organellar oligopeptidase (OOP) provides a complementary pathway for targeting peptide degradation in mitochondria and chloroplasts, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) E3761–E3769.
[76] K.A. Johnson, S. Bhushan, A. Stahl, B.M. Hallberg, A. Frohn, E. Glaser, T. Eneqvist, The closed structure of presequence protease PreP forms a unique 10,000 Å chamber for proteolysis, EMBO J. 25 (2006) 1977–1986.
[77] N. Mzhavia, Y.L. Berman, Y. Qian, L. Yan, L.A. Devi, Cloning, expression, and characterization of human metalloprotease 1: a novel member of the pitrilysin family of metalloendoproteases, DNA Cell Biol. 18 (1999) 369–380.
[78] C.M. Pinho, B.F. Bjork, N. Alikhani, H.G. Backman, T. Eneqvist, L. Fratiglioni, E. Glaser, C. Graff, Genetic and biochemical studies of SNPs of the mitochondrial A beta-degrading protease, hPreP, Neurosci. Lett. 469 (2010) 204–208.
[79] K. Hensley, N. Hall, R. Subramaniam, P. Cole, M. Harris, M. Aksenov, M. Aksenova, S.P. Gabbita, J.F. Wu, J.M. Carney, et al., Brain regional correspondence between Alzheimer's disease histopathology and biomarkers of protein oxidation, J. Neurochem. 65 (1995) 2146–2156.
[80] M. Manczak, T.S. Anekonda, E. Henson, B.S. Park, J. Quinn, P.H. Reddy, 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 (2006) 1437–1449.
[81] P.F. Teixeira, C.M. Pinho, R.M. Branca, J. Lehtio, R.L. Levine, E. Glaser, In vitro oxidative inactivation of human presequence protease (hPreP), Free Radic. Biol. Med. 53 (2012) 2188–2195.