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Biochemical and Biophysical Research Communications 328 (2005) 1–5
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Breakthroughs and Views

Widespread γ-secretase activity in the cell, but do we need it at the mitochondria?

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Received 20 December 2004
Available online 1 January 2005

Abstract

γ-Secretase cleavage of the amyloid precursor protein already subjected to a prior β-secretase cleavage generates β-amyloid (Aβ) peptide fragments, which are major constituents of the amyloid plagues found in Alzheimer's disease brain tissues. γ-Secretase activity and components of the γ-secretase complex are found in the endoplasmic reticulum-Golgi intermediate compartment, the Golgi, the *trans*-Golgi network, the plasma membrane, the endosomal–lysosomal system and recently, the mitochondria. Aβ fragments have been shown to be neurotoxic, leading to mitochondrial dysfunction and enhanced apoptotic cell death. However, if Aβ fragments are indeed detrimental to neurons, the widespread presence of enzymatic activity that would result in their generation in the cell appears to make little sense. The presence of a γ-secretase complex in the mitochondrion, an organelle that is particularly susceptible to Aβ toxicity, is even more puzzling. Emerging evidence suggests that both secreted and intracellular Aβ fragments have endogenous functions. Also, while the fibrillogenic $A\beta_{1-42}$ is clearly neurotoxic, the more abundant and soluble $A\beta_{1-40}$ is an antioxidant and could potentially be neuroprotective in several ways. A "physiological" amount of $A\beta_{1-40}$ production by cellular γ-secretase activity may be part of the neuron's natural counter against oxidative damage, in addition to endogenous roles in neuronal survival and modulation of synaptic transmission. In any case, whether Aβ is produced locally in the mitochondria and the function for mitochondrial Aβ, if produced, is yet unclear.

Keywords: Apoptosis; Alzheimer's disease; BACE-1; β-Amyloid; Mitochondria

Neurofibrillary tangles and extracellular amyloid plaques are distinct pathological features of Alzheimer's disease (AD). Extracellular plaques are made from aggregation of beta-amyloid (Aβ) peptide [1] generated from proteolytic cleavages of the amyloid precursor protein (APP) [2]. Aβ production from APP occurs via a two-step proteolytic process [3,4]. First, the β-site APP cleaving enzyme (BACE-1), a member of the pepsin family of aspartyl proteases, cleaves APP to generate a membrane bound C-terminal fragment. Subsequent cleavage by a γ-secretase activity generates peptides mainly of either 40 or 42 amino acids in length termed $A\beta_{1-40}$ and $A\beta_{1-42}$. Peptides of other lengths had been documented, the latest reported being $A\beta_{1-46}$ [5].

The γ-secretase activity responsible for the generation of Aβ is to be located in a complex which mediates a rather peculiar intramembrane proteolytic event (termed regulated intramembrane proteolysis or RIP) [6]. The catalytic core apparently resides on presenilins (PS) 1 or 2, but amyloidogenic activity requires three other proteins: nicastrin, anterior pharynx-defective phenotype (APH-1), and PEN-2 (PS-enhancer) [7]. Co-expression of all four of the above is required for the full reconstitution of γ-secretase activity in a naïve cell such as *Saccharomyces cerevisiae* [8].

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0006-291X/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbrc.2004.12.131

γ-Secretases everywhere?

With the cloning of the presenilins [9], accumulating evidence leaves little doubt that these molecules are essential for the γ-secretase activity [10]. Production of Aβ has been documented from various subcompartments of the cell [11]. Neurons and neuronal-like cells produce a good amount of intracellularly accumulated $A\beta_{1-42}$ at the ER-Golgi boundary (best described as the ER-Golgi intermediate compartment or ERGIC) [12,13]. The *trans*-Golgi network (TGN) produces secreted $A\beta_{1-40}$ and $A\beta_{1-42}$ [13–15]. Aβ production may also occur at the plasma membrane and the endosomal/lysosomal compartments [16–18]. Presenilins were first localized to the ERGIC [19]. Several recent papers have now demonstrated the presence of functional PS containing complexes at the *trans*-Golgi network [20], lipid rafts of post-golgi/endosome membranes [21], the plasma membrane [22], as well as, intriguingly, the mitochondria [23].

Confronted with this expanding number of places in the cell where one could find γ-secretase complexes, the question one might ask is the following. If Aβ is indeed a toxic byproduct of APP metabolism, why should the cell harbor such a widespread γ-secretase activity? Would that not be liken to setting a bomb that would slowly but steadily drive susceptible cells like neurons towards a timed demise?

One way around this apparent paradox is that Aβ generation by γ-secretase requires prior β-secretase cleavage. Thus, if BACE-1 activities are rather confined or restricted to particular locations in the cell, the more widespread γ-secretase activity would not be that detrimental. BACE-1, like the APP, traverses the secretory pathway and tends to cluster within plasma membrane lipid rafts [24]. From the plasma membrane, BACE-1 can be internalized to endosomal compartments. The similarity between the membrane traffic itinerary of APP and BACE-1 would indicate that plasma membrane and endosome are the major sites of BACE-1 cleavage of APP. BACE-1 is synthesized as a pre-proenzyme and is activated by a furin-like protease. It is not particularly clear how early along the exocytic pathway this activation occurs.

$A\beta_{1-42}$ production in $PS1/PS2^{-/-}$ cells at least appears to occur in the very early part of the secretory pathway [25]. Since BACE-1 activity is necessary for generation of $A\beta_{1-42}$, this is an evidence for the earlier becoming active fairly early upon its entrance of the exocytic pathway. There is also evidence for BACE-1-independent proteolytic activity in the regulated exocytic pathway, particularly that of cysteine proteases, in Aβ generation [26]. In any case, it does seem that APP could potentially be processed to generate Aβ at multiple locations of the exocytic and endocytic pathway. In saying this, it should be noted that the membrane topology of the APP and the secretase cleavage sites dictates that Aβ, if produced, would either be extracellular or lumenal and not cytosolic. It is not yet clear how lumenal Aβ affects cytoplasmic components of the cell. It should also be noted that the molecular nature of PS-independent γ-secretase activity [25,27] is unclear and evidence for their existence had been disputed [28,29].

Aβ-toxic or trophic?

According to the amyloid hypothesis, Aβ is a key causative agent of AD. That amyloid plaques are detrimental to neurons has been known for some time and is not in doubt, although there are theories which suggest that these are merely inactive reservoirs in equilibrium with smaller, perhaps more soluble, neurotoxic complexes [30]. Fibrillated and aggregated Aβ present extracellularly is not merely toxic to neurons, but to cells in general, as it is a pro-oxidant. Production of H_2O_2 and peroxidation of membrane lipid are central to its toxicity [31–33]. It is also realized recently that intracellular accumulation of Aβ in neurons is a prelude to the extracellular plaque, and neuronal death begins with that [34,35]. Mechanistically, Aβ-induced neuronal death has been attributed to the engagement of tumor necrosis factor receptor (TNFR1) [36] and involves the classical intrinsic apoptotic pathway [37] as well as less well-defined, caspase-4-dependent mechanisms [38].

On the other hand, Aβ was found in brain tissues and cerebrospinal fluid, and shown to be a normal product of neuronal metabolism [39–41]. Many workers have since found that a physiological concentration (nanomolar quantities) of $A\beta_{1-40}$, instead of being a pro-oxidant, has in fact anti-oxidative (particularly metal (Cu and Fe)-induced oxidation) functions. Accumulating evidence also suggests that the real culprit within the cell (particularly human neurons) is $A\beta_{1-42}$ and not $A\beta_{1-40}$ [3]. In fact, the latter may even act to counter the damage induced by the former both in vitro and in vivo [42]. That $A\beta_{1-42}$ but not $A\beta_{1-40}$ induced neuronal cell death when introduced intracellularly by microinjection or DNA construct-based expression are definitive experiments in support of this notion [37]. These form and context-dependent dual pro- and anti-oxidative properties of Aβ have been excellently reviewed in detail in recent articles, with the peptide's dichotomous properties being likened to those of a chameleon [43,44].

Enigmatically, although both targeted disruption of BACE-1 and APP do not result in embryonic lethality or decrease neuronal viability, Aβ production is apparently required for neuronal viability. Secretase inhibitors and, amazingly, a monoclonal antibody which binds Aβ reduces the viability of cortical neurons. The neurotoxic effects of these reagents could be reversed by nanomolar quantities of $A\beta_{1-40}$, but not $A\beta_{1-42}$ or the synthetic

$A\beta_{25\text{-}35}$ [45]. Secretase inhibitors will reduce both intracellular and secreted Aβ, but the antibody effect indicates that secreted Aβ is likely to be neuroprotective in some manner.

Aβ and modulation of synaptic function

AD is primarily manifested by neurological symptoms resulting from hippocampal synaptic dysfunction before neuronal cell death becomes obvious [46]. Such synaptic failures may be caused by soluble Aβ oligomers [47]. A direct physiological for Aβ in modulating synaptic transmission has been demonstrated recently [48]. The formation and secretion of Aβ from hippocampal slide cultures is modulated by neuronal activity, which appear to act through the BACE-1 mediated step rather than that mediated by γ-secretase. Aβ, in turn, depresses glutamate receptor mediated fast excitatory synaptic transmission but not inhibitory transmission by GABA receptors, importantly, in a non-cell autonomous manner. These ex vivo data are very informative as they point towards a mechanism as to how intracellular or extracellular Aβ may affect excitatory synaptic efficacy, thus providing an explanation for the neurological defects in early AD. Furthermore, as the authors surmised, modulation of Aβ production by neuronal activity could be a feedback mechanism that regulates the effect of Aβ on synaptic transmission. The diminishment of such mechanisms with aging and neuronal death in a population would likely contribute towards AD progression.

Localized production of Aβ at the mitochondria?

The recent findings summarized above speak well for $A\beta_{1\text{–}40}$ having an endogenous function, especially in neurons. But, is there a physiological need to produce Aβ at the mitochondria? Before exploring what good might that do for the cell, let us take a step back to first examine the possibility of mitochondrial localized Aβ production.

The latest findings indicate that nicastrin has dual targeting sequence at its N-terminus, with a stretch of amino acids downstream of the first 32 (which is an ER-targeting signal sequence) resembling that of a mitochondrial matrix targeting presequence [23]. Other than nicastrin, PS1 has been shown earlier to be also present in the mitochondria [49]. The mechanism of mitochondrial import does not permit the translocation of preformed, large complexes and it is clear that mitochondrial PS-1, APH-1, and PEN-2 are individually targeted to the organelle. In the mitochondria, these components come together to result in measurable mitochondrial-associated γ-secretase activity [23]. Apparently, this activity is largely associated with the mitochondrial inner membrane, where the majority of immunogold signals of PS1 [49] and nicastrin [23] are found. If the mitochondrial targeting signal of nicastrin functions like a presequence, it is also likely to have been imported into the matrix and reinserted into the inner membrane with the aid of the OXA complex. Interestingly, it was shown earlier that APP itself, reminiscent of nicastrin, could be targeted to the mitochondria by a presequence-like targeting sequence downstream of its ER signal sequence [50]. However, the topology of APP at the mitochondria, as delineated by in vitro assays, is rather peculiar. An acidic domain (amino acids 220–290) of APP appears to cause an arrest in membrane translocation, resulting in the protease protection of a 22 kDa N-terminal portion, but with a C-terminal 73 kDa portion of the polypeptide exposed cytoplasmically. Such an orientation of mitochondrially targeted APP means that its transmembrane domain, which contains the γ-secretase cleavage sites, would be inaccessible to the intramembrane proteolytic activity of the mitochondrial complex at the inner membrane. This, coupled to a lack of evidence for BACE-1 activity at the mitochondria, would speak against localized production of Aβ within the membranes of this organelle, even when the level of APP targeting to it is intensified under pathological conditions.

However, that a fraction of APP (or even the BACE-1 processed APP C-terminal fragment) may be "correctly" inserted into the inner membrane of the mitochondria could not be ruled out at the present. If localized Aβ production at the mitochondria does occur physiologically, what purpose might that serve? Aβ has in fact been shown to interact with two intracellular targets that are localized to the mitochondria. The first, found by a yeast 2-hybrid screen in 1997, is the Aβ-binding alcohol dehydrogenase (ABAD, also known as ERAB) [48]. ABAD is a member of the family of short chain dehydrogenase/reductases and appears to be a direct link between Aβ and mitochondrial toxicity in AD [51]. Aβ's direct binding to ABAD impairs its ability to engage the cofactor nicotinamide adenine dinucleotide. When either or both are abundant, this interaction somehow leads to reactive oxygen species leakage and increases neuronal oxidative stress characteristic of AD [52]. Whether Aβ–ABAD interaction occurs at more physiological settings and whether this is required for, or the modulation of, ABAD's activity is unclear. ABAD may have more general connections to mitochondrial dysfunction and neurodegeneration, as it is down-regulated in Parkinson's disease patients and appears to counter the toxicity of MPTP [53]. It is possible that Aβ–ABAD interaction at physiological concentrations may actually be beneficial, or Aβ may regulate the activities and functions of ABAD.

Another mitochondrial protein that has been recently shown to interact with Aβ is HtrA2/Omi [54], a pro-

apoptotic serine protease that, interestingly, was earlier shown to also interact with PS1 [55]. HtrA2/Omi is released into the cytosol from the mitochondria upon apoptotic stimuli. It functions by antagonizing the inhibitors of apoptosis (IAPs) and is implicated in neuronal degeneration [56]. Aβ binds to the C-terminal PDZ domain of HtrA2/Omi, and when expressed intracellularly, co-precipitates the cytosolic form of the latter [54]. It is unknown whether Aβ-HtrA2/Omi interaction occurs within the mitochondria, and whether this interaction regulates HtrA2/Omi's release and subsequent activity. However, it is conceivable that regulating the apoptotic function of HtrA2/Omi may be related to Aβ 's neuroprotective property.

Epilogue

That APP knockout mice lack a revealing phenotype, Aβ's physiological presence in brain tissues, and the widespread γ-secretase activity in the cell are all enigmatic and engaging issues when one ponders on the pathophysiology of AD. As we know more about Aβ's physiological functions and how these may become pathological with genetic factors, metabolic disorders, and aging associated processes in the neuron, we shall be presented with clues as to how we may delay this change. On the other hand, this new knowledge may also make us reconsider and even redesign therapeutic approaches that target γ-secretase and Aβ production [57,58].

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