Seminars in Cell & Developmental Biology 20 (2009) 175–182

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

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

Review

Function, regulation and therapeutic properties of β-secretase (BACE1)

Michael Willem*, Sven Lammich*, Christian Haass

Center for Integrated Protein Science Munich, Adolf-Butenandt-Institute, Department of Biochemistry, Laboratory for Neurodegenerative Disease Research, Ludwig-Maximilians-University, 80336 Munich, Germany

ARTICLE INFO

Article history:
Available online 20 January 2009

Keywords:
Alzheimer's disease
Aβ
APP
BACE1
Neuregulin
Secretase

ABSTRACT

β-Secretase (β-site amyloid precursor protein cleaving enzyme 1; BACE1) has been identified as the rate limiting enzyme for amyloid-β-peptide (Aβ) production. Aβ is the major component of amyloid plaques and vascular deposits in Alzheimer's disease (AD) brains and believed to initiate the deadly amyloid cascade. BACE1 is the principle β-secretase, since its knock-out completely prevents Aβ generation. BACE1 is likely to process a number of different substrates and consequently several independent physiological functions may be exerted by BACE1. Currently the function of BACE1 in myelination is best understood. BACE1 cleaves and activates Neuregulin-1 and is thus directly involved in myelination of the peripheral nervous system during early postnatal development. However, additional physiological functions specifically within the central nervous system are so far less understood. BACE1 is upregulated in at least some AD brains. Multiple cellular mechanisms for BACE1 regulation are known including post-transcriptional regulation via its 5′-untranslated region, microRNA and non-coding anti-sense RNA. BACE1 is a primary target for Aβ lowering therapies, however the development of high affinity bio-available inhibitors has been a major challenge so far.

Contents

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease worldwide. The major pathological hallmarks of AD are intracellular neurofibrillary tangles, which consist mainly of the hyperphosphorylated tau protein and extracellular amyloid plaques [1]. Amyloid plaques are composed predominantly of the amyloid-β-peptide (Aβ), a hydrophobic peptide of 39–43 amino acids [2,3]. Aβ is liberated upon endoproteolytic processing of the amyloid precursor protein (APP) by consecutive cleavages of β-secretase and γ-secretase (Fig. 1). An inherited mutation which results in the KM to NL double exchange at the β-secretase cleavage site in APP, the so called Swedish APP mutant (APPswe) was described to increase the efficiency of β-cleavage [4,5]. β-Secretase was discovered in 1999 independently by a number of different groups [6–10]. Therefore a confusing nomenclature exists in the literature. Accordingly, β-secretase has been called BACE1 (for β-site APP cleaving enzyme 1) [6], memapsin 2 [10] or Asp 2 [7,9]. We hereafter refer to β-secretase as BACE1. BACE1 is a member of the pepsin-like family of aspartyl proteases. It is a type I membrane protein, which contains the characteristic dual active site motif (D-T/S-G-T/S) of aspartic proteases in its ectodomain [6,11]. Mutations in either one of the two active site motifs result in complete loss of function [7,12]. BACE1 is ubiquitously expressed with highest levels in brain and pancreas. BACE1 activity in pancreas is low due to the generation of alternatively spliced transcripts, which produce BACE1 variants with reduced proteolytic activity [13]. In

Abbreviations: AD, Alzheimer's disease; ADAM, a disintegrin and metalloprotease; APP, amyloid precursor protein; Aβ, amyloid-β-peptide; BACE1, β-site APP cleaving enzyme 1; NRG1, Neuregulin-1; PS, presenilin.

* Corresponding authors. Tel.: +49 89218075462/89218075484; fax: +49 89218075415.
E-mail addresses: mwillem@med.uni-muenchen.de (M. Willem), slammich@med.uni-muenchen.de (S. Lammich).

1084-9521/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.semcdb.2009.01.003

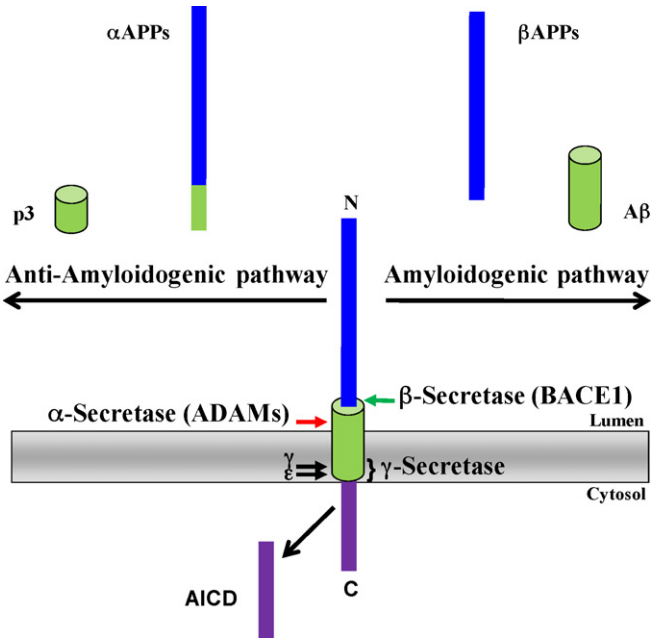

Fig. 1. Processing of APP. Proteolytic processing of APP occurs by two alternative pathways: BACE1 dependent cleavage results in the release of soluble APP (β-APPs). The C-terminal membrane-bound stub is subjected to intramembraneous proteolysis by γ-secretase in a stepwise manner at the ε- and γ-site which liberates the intracellular domain of APP (AICD) into the cytoplasm and Aβ into the lumen. Alternatively the smaller fragment p3 can be released in a similar way by concerted α- and γ-secretase mediated proteolysis. The anti-amyloidogenic pathway is initiated by the α-secretases ADAM9, ADAM10 or ADAM17.

contrast high BACE1 enzymatic activity was found in human brain extracts. This is consistent with the finding that neurons produce the highest levels of Aβ [8,14]. BACE1 cleaves APP into two fragments. The N-terminal soluble β-APPs is released upon shedding by BACE1. A C-terminal fragment (C99) is retained in the membrane, which is the immediate precursor for Aβ generation (Fig. 1). γ-Secretase, a protein complex consisting of nicastrin, APH-1 (anterior pharynx-defective phenotype-1), PEN-2 (PS enhancer 2) and presenilin (PS), cleaves C99 in a stepwise manner within its transmembrane domain at the ε-, ζ- and γ-site [3,15]. These cleavage events generate the APP intracellular domain (AICD) and several species of Aβ. If AICD serves as a transcriptional regulator like other γ-secretase cleavage products is currently under debate [16–20]. The liberated hydrophobic Aβ peptide forms toxic oligomers, which induce the amyloid cascade and probably cause cognitive impairment and neuronal loss. Aβ accumulation is counterbalanced by its proteolytic degradation and drainage from the brain [21–23].

APP can not only be shed by BACE1 but it is also cleaved in the middle of the Aβ domain by α-secretase, thereby precluding the formation of Aβ (Fig. 1). Three members of the ADAM (a disintegrin and metalloprotease) family of metalloproteases are described to have α-secretase activity, namely ADAM9, ADAM10 and ADAM17 [24–26]. The processing of APP by α-secretase generates the soluble α-APPs ectodomain, which may have neuroprotective and neurotrophic properties [27] and a membrane-bound C-terminal fragment (C83). Whether the truncated β-APPs lacks this function is currently unclear. C83 is further cleaved by γ-secretase, producing the non-amyloidogenic p3 as well as AICD. Together with BACE1, another membrane-bound aspartyl protease with substantial sequence homology to BACE1, termed BACE2 (memapsin 1 or Asp 1) was discovered [28–31]. However, BACE2 seems to function primarily as an α-secretase-like activity [29,31,32] and is preferentially expressed in non-neuronal cells [28]. BACE2 is clearly not involved in Aβ generation as an alternative β-secretase activity [29,31,32], therefore in the following we will focus on BACE1 only.

1. Maturation and cellular localization of BACE1

The identification of the aspartyl protease BACE1 as β-secretase allowed the rapid characterization of this enzyme. Purified BACE1 has an optimal enzymatic activity at an acidic pH of approximately 4.5, which reflects its primary site of action inside the cell, i.e. in acidified endosomes [6,14,33]. However, APP containing the Swedish mutation is, due to the better cleavage site, already cleaved within the Golgi apparatus, thus allowing BACE1 to outcompete anti-amyloidogenic processing by α-secretase activities [34,35]. If BACE1 principally exists as a monomeric enzyme or as a dimer is not well understood. However, in brain tissue of mice and humans BACE1 forms homodimers. Interestingly, such homodimers exert a higher enzymatic activity than monomeric BACE1 [36,37]. BACE1 is synthesized in the endoplasmatic reticulum (ER) as an immature proenzyme with a molecular weight of 60 kDa. BACE1 then rapidly matures to the 70 kDa form. Maturation involves disulfide bridge formation, N-glycosylation, carbohydrate sulfation, propeptide removal by prohormone protein convertases like Furin and palmitoylation at its junction of the trans-membrane and cytoplasmic domain [38–43]. While deletion of the glycosylation sites has a significant impact on BACE1 activity [44], removal of the prodomain does not diminish the enzymatic activity of BACE1 towards its substrate APP to a great extent [43,45]. After its maturation in the ER and the Golgi apparatus BACE1 is transported to the plasma membrane. It is discussed that Aβ generation is increased in lipid rafts because of colocalization of BACE1 and its substrate APP [46–49]. However, a recent study suggests that the activity of BACE1 is independent of its palmitoylation and thereby can occur in non-raft subdomains of the plasma membrane [50]. Similar to APP, BACE1 is internalized from the plasma membrane to early endosomes, the main compartment of Aβ generation [33]. The internalization is driven primarily by the di-leucine sorting signal within the C-terminus (DISLLK) [39,51]. BACE1 is recycled from early endosomal compartments to the trans-Golgi-network (TGN). The phosphorylation of a single serine residue (S498) in the C-terminus near to the di-leucine motif of BACE1 is required for this event. Wild type BACE1 and a S498D carrying BACE1 mutant which mimics phosphorylated BACE1 are efficiently retrieved from early endosomes to the TGN, whereas the non-phosphorylatable mutant BACE1 S498A is retained in early endosomes [52]. The recycling step depends on Golgi-localized γ-ear containing ADP (GGA) ribosylation factor binding proteins [53–55]. GGA1 mediated rerouting from endosomes to the TGN and recycling to the plasma membrane lead to a longer half-life of BACE1. In addition, it was reported that phosphorylated BACE1 could be transported in a GGA3 dependent manner from endosomes to lysosomes where BACE1 can be degraded [56,57]. Finally, BACE1 undergoes proteolytic degradation by the proteasome [58] although the physiological relevance of BACE1 processing by the proteasome is unclear.

In neurons BACE1 is transported to axonal membrane surfaces and is most likely localized to pre-synaptic terminals in vivo [59,60]. Thus, axonally derived Aβ is eventually released from axon terminals [60]. In support of this Kamenetz et al. described an upregulation of BACE1 by synaptic activity and they put forward a role for Aβ, which in a feedback loop might regulate BACE1 levels via modulation of synaptic activity [61].

2. BACE1 substrates

BACE1 knock-out mice fail to produce any Aβ, thus BACE1 is the sole enzyme with a bonafide β-secretase activity. These mice