Advances in Biological Regulation xxx (2016) 1–6

Contents lists available at ScienceDirect

Advances in Biological Regulation

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

Aberrant proteolytic processing and therapeutic strategies in Alzheimer disease

Taisuke Tomita*

Laboratory of Neuropathology and Neuroscience, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo 113-0033, Japan

ARTICLE INFO

Article history:
Received 9 December 2016
Received in revised form 24 December 2016
Accepted 4 January 2017
Available online xxx

Keywords:
Alzheimer disease
Amyloid-β peptide
Membrane protein
Protease
Secretase
Degradation

ABSTRACT

Amyloid-β peptide (Aβ) and tau are major components of senile plaques and neurofibrillary tangles, respectively, deposited in the brains of Alzheimer disease (AD) patients. Aβ is derived from amyloid-β precursor protein that is sequentially cleaved by two aspartate proteases, β- and γ-secretases. Secreted Aβ is then catabolized by several proteases. Several lines of evidence suggest that accumulation of Aβ by increased production or decreased degradation induces the tau-mediated neuronal toxicity and symptomatic manifestations of AD. Thus, the dynamics of cerebral Aβ, called as "Aβ economy", would be the mechanistic basis of AD pathogenesis. Partial loss of γ-secretase activity leads to the increased generation of toxic Aβ isoforms, indicating that activation of γ-secretase would provide a beneficial effect for AD. After extensive discovery and development efforts, BACE1, which is a β-secretase enzyme, has emerged as a prime drug target for lowering brain Aβ levels. Recent studies revealed the decreased clearance of Aβ in sporadic AD patients, suggesting the importance of the catabolic mechanism in the pathogenesis of AD. I will discuss with these proteolytic mechanisms involved in the regulation of Aβ economy, and development of effective treatment and diagnostics for AD.

Contents

* Corresponding author. Laboratory of Neuropathology and Neuroscience, Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.
E-mail address: taisuke@mol.f.u-tokyo.ac.jp.

http://dx.doi.org/10.1016/j.jbior.2017.01.001
2212-4926/

1. Introduction

Alzheimer disease (AD) is characterized by extensive neuronal loss and the appearance of two types of neuropathological hallmarks; senile plaques and neurofibrillary tangles (Goedert, 2015; Selkoe and Hardy, 2016; Sperling et al., 2014). Senile plaques present extracellularly and consist mainly of amyloid-β protein (Aβ). Aβ is produced from its precursor called amyloid precursor protein (APP) through sequential cleavage by β- and γ-secretases (De Strooper et al., 2010) (Fig. 1). Neurofibrillary tangles are comprised of intraneuronal aggregation of microtubule-binding protein, tau. Importantly, genetic mutations in *APP* gene found in patients of the dominantly inherited form of familial AD cause increased production and/or aggregation of Aβ (Selkoe and Hardy, 2016). Moreover, genes encoding multipass membrane proteins called presenilin (PS) 1 and 2 were identified in familial AD patients (Sherrington et al., 1995). These mutations alter the γ-secretase-mediated cleavage of APP, leading to increased production of the more aggregation-prone form of Aβ (Borchelt et al., 1996; Tomita et al., 1997). *APP* locus duplication was also identified in autosomal dominant early-onset AD cases (Rovelet-Lecrux et al., 2006). And recently, a rare coding mutation A673T in the *APP* gene that reduces the β-secretase-mediated cleavage has been identified in the elderly without AD as a protective allele (Jonsson et al., 2012), supporting the central role of Aβ in the development of AD. In contrast, aberrant tau aggregates are present not only in AD, but several neurodegenerative disease such as progressive supranuclear palsy, Pick's disease, corticobasal degeneration or frontotemporal dementia, the latter being characterized by massive neuronal loss and the formation of tangles without deposition of Aβ (Iqbal et al., 2016). Tau is a phosphoprotein that promotes the assembly and stabilization of microtubules. Tau also interacts with several proteins such as phospholipase C to regulate intracellular signaling involved in the neuronal functions (Gunawardana et al., 2015; Yang et al., 2016). Aggregated tau undergoes hyperphosphorylation, which promotes dissociation of tau from the microtubules and self-aggregation. Importantly, mutations in tau gene are linked to autosomal dominant form of frontotemporal dementia, indicating that tau pathology correlates with neuronal death. In fact, biomarker observational studies suggest a pathological model of AD that brain Aβ deposits early, before neurodegeneration biomarker changes (i.e., brain atrophy and increased cerebrospinal fluid (CSF) tau) and clinical symptoms occur (Jack et al., 2010). Longitudinal assessment of neuroimaging and clinical markers in autosomal dominant familial AD patients also support this model (Bateman et al., 2012; Reiman et al., 2012). Finally, tangle pathology was induced/exacerbated by aggregated Aβ in model animals (Gotz et al., 2001; Lewis et al., 2001), and tau was required for the Aβ mediated neurotoxicity (Roberson et al., 2007). Thus, these observations clearly suggest that Aβ is an initiator molecule of AD pathogenesis, and tau is associated with neuronal dysfunction and cell death (Sperling et al., 2014).

2. Proteolytic processing of APP by β- and γ-secretases

APP is processed by the non-amyloidogenic or amyloidogenic pathway (De Strooper et al., 2010). In the non-amyloidogenic pathway, APP is first cleaved at its juxtamembrane region by α-secretase, leading to generation of the soluble N-terminal fragment sAPPα and C-terminal stub called C83. A disintegrin and metalloprotease 10 (ADAM10) is the main enzyme responsible for α-secretase activity (Kuhn et al., 2010). In the amyloidogenic pathway, β-site APP-cleaving enzyme 1 (BACE1) endoproteolyzes APP at ectodomain, yielding the secreted sAPPβ and a longer C-terminal fragment, C99 (Yan, 2016; Yan and Vassar, 2014). Then both C83 and C99 are subjected to intramembrane cleavage by γ-secretase to release extracellularly p3 or Aβ, respectively. As BACE1 is a single-span membrane-anchored aspartic protease expressed in neuronal cells, Aβ is mainly generated from neurons. γ-Secretase-mediated cleavage occurs several cell types, and generates heterogeneity in the C-terminal length of Aβ, mainly producing Aβ40 and Aβ42. Aβ42 is the most toxic and aggregation-prone Aβ species and is the predominant species deposited in AD brains (Iwatsubo et al., 1994). Notably, it took about 10 years to gain a comprehensive understanding of γ-cleavage at molecular level, because the γ-secretase mediated hydrolysis of APP should be occurred within the transmembrane domain (TMD) that is embedded in the hydrophobic environment. Several biochemical, cell

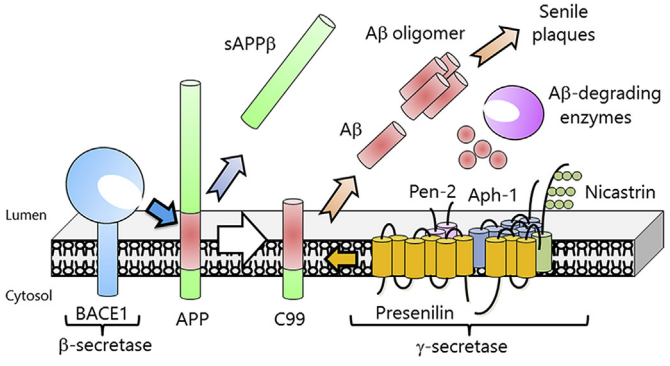

Fig. 1. Schematic diagram of proteolytic processing of APP and Aβ.
β-Secretase/BACE1 cleaves APP to generate sAPPβ and C99, the latter being further processed by γ-secretase. These sequential cleavages result in the production of Aβ, which is a main component of the senile plaque. The minimal γ-secretase complex is comprised of PS, nicastrin, Aph-1 and Pen-2. Aβ is then metabolized by proteolytic processing by Aβ-degrading enzymes and other catabolic processes (i.e., phagocytosis, passive and active transport, diffusion).

Please cite this article in press as: Tomita, T., Aberrant proteolytic processing and therapeutic strategies in Alzheimer disease, Advances in Biological Regulation (2016), http://dx.doi.org/10.1016/j.jbior.2017.01.001