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Beyond the signaling effect role of amyloid–β_{42} on the processing of AβPP, and its clinical implications

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Abstract

Alzheimer's disease (AD) currently has over 6 million victims in the USA, alone. The recently FDA approved drugs for AD only provide mild, transient relief for symptoms without addressing underlying mechanisms to a significant extent. Basic understanding of the activities of the amyloid β peptide (Aβ) and associated proteins such as β–site AβPP-cleaving enzyme 1 (BACE1) is necessary to develop effective medical responses to AD. In this issue, Tabaton et al have presented a model of both non–pathological and pathological Aβ activity and suggest potential therapeutic pathways based on their proposed framework of Aβ acting as the signal that induces a kinase cascade, ultimately stimulating transcription factors that upregulate genes such as BACE1. We respond by presenting evidence of Aβ's other activities, including protection against metal–induced reactive oxidizing species (ROS), modification of cholesterol transport, and potential activity as a transcription factor in its own right. We touch upon clinical implications of each of these functions and highlight the currently unexplored implications of our suggested novel function of Aβ as a transcription factor. Aβ appears to be a highly multifunctional peptide, and any or all of the pathways it engages in is a likely candidate for anti–AD drug development.

Keywords

Aging; Alzheimer's disease; amyloid beta peptide; clinical trial; dementia; drug discovery; gene regulation; molecular pharmacology; signaling; transcription factor; treatment

Introduction

Alzheimer's disease (AD) currently afflicts 6.5 million Americans (5.1 million over the age of 65) and is projected to increase to between 11 and 16 million by 2050 ("2009 Alzheimer's disease facts and figures," 2009). Over $4 billion in revenues are currently generated by the five US federal drug agency (FDA)–approved drugs: Aricept (Donepezil, Pfizer), Cognex (Tacrine, Parke–Davis), Razadyne (Galantamine, Ortho–McNeil–Janssen), Exelon (Rivastigmine, Novartis), and Namenda (Memantine, Forest). These current

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therapies for AD provide only mild, transient symptomatic relief. A significant unmet need exists for improved drugs, which are based on novel molecular targets that modify the underlying course and address the etiology of the disease. To design drugs for this end, the fundamental activities of molecules such as amyloid–β peptide (Aβ), Aβ precursor protein (AβPP), β–site AβPP–cleaving enzyme 1 (BACE1)—the β–secretase molecule, and presenilin–1 (PSEN1)—a necessary component of γ–secretase activity—must be elucidated. The Aβ peptide is of particular interest, as it is the center of the "amyloid cascade" hypothesis—the currently dominant model of AD etiology. In addition, understanding of normal Aβ clearance pathways, such as insulin degrading enzyme (IDE), is important for therapeutic use Aβ metabolism (Eckman and Eckman, 2005).

The processing of AβPP into Aβ requires two enzymatic activities. AβPP is first cleaved by β–secretase, producing soluble AβPP and a cell–membrane bound fragment (Lahiri, et al., 2003). This fragment is further cleaved by γ–secretase to produce Aβ and the AβPP intracellular domain (AICD). AICD has been shown to function in regulation of gene transcription (Konietzko, et al., 2010), indicating an important non pathogenic role for γ–secretase. However, the Aβ generation is a minority AβPP processing pathway. The majority of AβPP is cleaved by α–secretase, a large molecule complex that includes members of the ADAM protein family (Asai, et al., 2003). This pathway represents a neuroprotective route for AβPP processing (Kojro and Fahrenholz, 2005), and encouraging the α–secretase pathway may be clinically productive (Fahrenholz, 2007).

In "Signaling effect of amyloid–β_{42} on the processing of AβPP", Tabaton *et al* present a model of Aβ function and portray it primarily as an extracellular signaling peptide that begins a cascade which regulates both β– and γ–secretase activity, thus regulating both steps of its own cleavage from the Aβ precursor protein, AβPP. Their review presents another emerging picture of the state of knowledge regarding both Aβ dysfunction and BACE1.

When summarizing the "normal" functions of Aβ, the authors stress a potential role as a signaling pathway partner to TrkA, MAPK, and JNK to the exclusion of most other potential functions. Similarities between Aβ and Notch are noted in the paper. The authors provide a more complete picture of Aβ dysfunction, highlighting its toxic and oxidative activities as individual subunits and oligomers, and its formation into amyloid plaque in AD brains. Each of these potential activities is of more than theoretical importance, since each lends itself to different therapeutic responses.

Aβ signaling and kinases

Tabaton et al emphasize a straightforward kinase pathway for Aβ function. The authors propose a model in which Aβ initiates a signaling cascade that may involve extracellular signal–related kinase (ERK), serine/threonine protein kinase, (Akt), phosphorylated c-Jun N-terminal kinase (pJNK), insulin receptor substrate (IRs), and/or G proteins, ultimately modifying the activity of transcription factors that, in turn, modify expression of the BACE1 gene. This route was proposed at least half a decade ago, specifically targeting JNK (Bogoyevitch, et al., 2004) based on the neuroprotective activity of JNK3 and association of JNK genes with diabetes and obesity, two conditions that are, themselves, associated with AD (Qiu, et al., 2007).

Aβ and metal chelators

Some functions they neglect include Aβ reducing metal charge states, such as reduction of copper (II) to copper (I) (White, et al., 1999). This suggests that Aβ may protect against metal–induced oxidative damage (Baruch-Suchodolsky and Fischer, 2009, Zou, et al., 2002). On the other hand, Aβ's suggested protective activity against metal–induced

oxidation points to a potential cause to explore for the contribution of Aβ to oxidative conditions, as it has been suggested that Aβ as antioxidant is transformed to Aβ as pro–oxidant specifically through its interaction with oxidizing metals (Kontush, 2001). This suggests exploration of chelating agents as a potential Aβ prophylactic or early therapy to administer during the stages of AD, including mild cognitive impairment (MCI).

Aβ and cholesterol transport

In addition, Aβ may control cholesterol transport (Igbavboa, et al., 2009, Yao and Papadopoulos, 2002). Addressing Aβ's potential role in cholesterol metabolism leads to the investigation of lipid–modifying drugs.

Aβ mediated regulation of BACE1

β–secretase activity provided by BACE1 is the rate–limiting step in the production of Aβ from AβPP (Vassar, 2001). Control of secretase activity, especially β–secretase could be a fruitful path toward limiting harmful effects of Aβ. To explore the secretase route, Tabaton et al present a brief discussion of the β–secretase protein, BACE1. Notably, BACE1 activity is the rate–limiting step in formation of Aβ from AβPP. The BACE1 gene promoter has been structurally and functionally characterized, and a 91bp proximal DNA fragment appears to be the minimal constitutive promoter region (Ge, et al., 2004, Lahiri, et al., 2006, Sambamurti, et al., 2004). Among the transcription factors associated with BACE1 regulation are YY1, SP1, and MEF2 (Dosunmu, et al., 2009, Lahiri, et al., 2006, Nowak, et al., 2006).

If some feedback mechanism were to exist between Aβ and BACE1, this could provide a powerful route to investigate Aβ–related pathogenesis. The authors have recently determined that BACE1 transcription is upregulated by addition of $A\beta_{1–42}$, but not by AICD (Giliberto, et al., 2009). They then speculate that the specific pathway of this upregulation is through JNK signaling, although their prior demonstration of JNK activity in BACE1 gene regulation does not show the activity of Aβ in that particular pathway (Tamagno, et al., 2009).

It is interesting to note that Tabaton, et al, cite a work by Ohyagi, et al, specifically the activation of the p53 promoter by intracellular Aβ (Ohyagi, et al., 2005). In addition, a p53 promoter–reporter clone containing a mutation at the Aβ binding site within the promoter produced reduced activation from intracellular Aβ (Ohyagi, et al., 2005). However, in building their model, Tabaton et al do not mention that the p53–related paper also demonstrated direct binding of DNA by Aβ, both *in vitro* by gel shift and *in vivo* by chromatin immune precipitation (ChIP) nor that altering the putative Aβ binding DNA motif altered induction of promoter activity by Aβ. Ultimately, all Aβ in the stimulation pathway proposed is either presumed to be extracellular or cytoplasmic, operating through G proteins or JNK. The earlier work demonstrated that Aβ could be induced to enter the nucleus (Ohyagi, et al., 2005), a localization that was not mentioned. Ohyagi et al's work has been further extended to confirm inducible nuclear localization for Aβ (Bailey and Lahiri, 2009), to specify the consensus DNA motif to which Aβ binds (Maloney, et al., 2006), and to show changes in activity of the AβPP promoter following treatment of cell cultures by Aβ in solution (Lahiri, et al., 2009). Indeed, the consensus Aβ–binding sequence has recently been found in the BACE1 promoter region, and two of the putative sites have been shown to bind Aβ *in vitro* (Lahiri, et al., 2010). This recent evidence is suggestive of Aβ's direct regulation of the BACE1 promoter, and, thereby, its own production, which need not be mediated through signaling intermediaries. Instead, our recent work strongly indicates that Aβ may function as a transcription factor in its own right, regulating not only BACE1, but also AβPP

and potentially other genes involved in Alzheimer's disease (Fig. 1A). Therapies based upon modifying Aβ's activity as a transcription factor would (Fig. 1B–C) be feasible but speculative at this stage. However, oral small interfering RNA (siRNA) has proven effective in downregulating systemic inflammatory responses (Aouadi, et al., 2009), and both siRNA and antisense oligonucleotides can be successfully delivered by oral route (Akhtar, 2009).

Clinical implications and drug targets of alternate Aβ functional pathways

The various exploratory routes suggested by each pathway related to Aβ production are summarized in Table 1. Tabaton et al appear to suggest that kinase modification is the most fruitful direction to choose, but this ignores four other potential avenues, each of which has varying degrees of evidentiary support. Unfortunately, the oral Akt inhibitor perifosine failed to diminish tumors as a sole oncological treatment agent (Gills and Dennis, 2009), raising questions about its potential efficacy in other pathways. Likewise, the mixed lineage kinase inhibitor CEP 1347 (mentioned as a potential agent to investigate by Bogoyevitch et al) did not delay disability in early Parkinson's disease (Wang and Johnson, 2008).

On the other hand, metal chelation has appeared to bear more clinical fruit. For example, the test drug PBT2, a derivative of the chelator clioquinol, has been shown to inhibit Aβ oligomer formation, disaggregate Aβ plaque, and neutralize Aβ toxicity (Ritchie, et al., 2004). The drug has been shown to restore cognitive function to AD model mice (Adlard, et al., 2008), and it has recently finished successful phase IIb trial (Lannfelt, et al., 2008).

Cholesterol modification also appears to be promising. Agents based on this pathway would include simvastatin, which has improved cerebral function and reversed toxic effects of Aβ in mouse models (Tong, et al., 2009). The drug D–4F, which mimics ApoA–I and can be orally administered, improves cognitive function in AD model mice (Handattu, et al., 2009) and reduces brain arteriole inflammation in LDL receptor–deficient mice (Buga, et al., 2006). Even dietary modification of fat and cholesterol intake has been shown to modify levels of intracellular Aβ in rodent models (Pallebage-Gamarallage, et al., 2009). A non–negligible role for intracellular Aβ in AD has been investigated and found to be of potential therapeutic value (Ohyagi, 2008).

Several secretase–modifying drugs have also been investigated. Preclinical studies of a β–secretase inhibitor CTS 21166 have also shown promising results (Panza, et al., 2009). The γ–secretase inhibitor LY450139 dihydrate is currently undergoing phase III trial. It has been shown to reduce Aβ synthesis without altering Aβ clearance (Bateman, et al., 2009). An especially promising route to investigate would be to not only reduce β–secretase activity but encourage the α–processing pathway. The drug etazolate is currently in phase IIb trial after having demonstrated precognitive and neuroprotective properties in rodent models (Marcade, et al., 2008).

Of particular theoretical interest would be pursuing the potential role of Aβ as a transcription factor. Given the variable nature of the Aβ–binding DNA motif (Lahiri, et al., 2009), appreciable specificity for promoter targets could be designed into DNA sequence–based therapies. However, the conclusion that Aβ is a multi–functional peptide cannot be reasonably avoided. Direct alteration of Aβ levels is likely to impact cholesterol metabolism, metal–induced ROS in the nervous system, and has organism–wide implications in regulation for an as–yet weakly characterized set of genes. It is certainly a worthwhile target to explore for prevention and treatment of AD. However, its involvement in an amazing variety of pathways and activities suggests that a multi–pronged approach may prove the most effective way to safely modify Aβ's potential pathogenic activity. In combination with the aforementioned approaches, the role of dietary and environmental factors and epigenetic

regulation of BACE1 and other genes, should also be considered (Lahiri and Maloney, 2010, Lahiri, et al., 2009).

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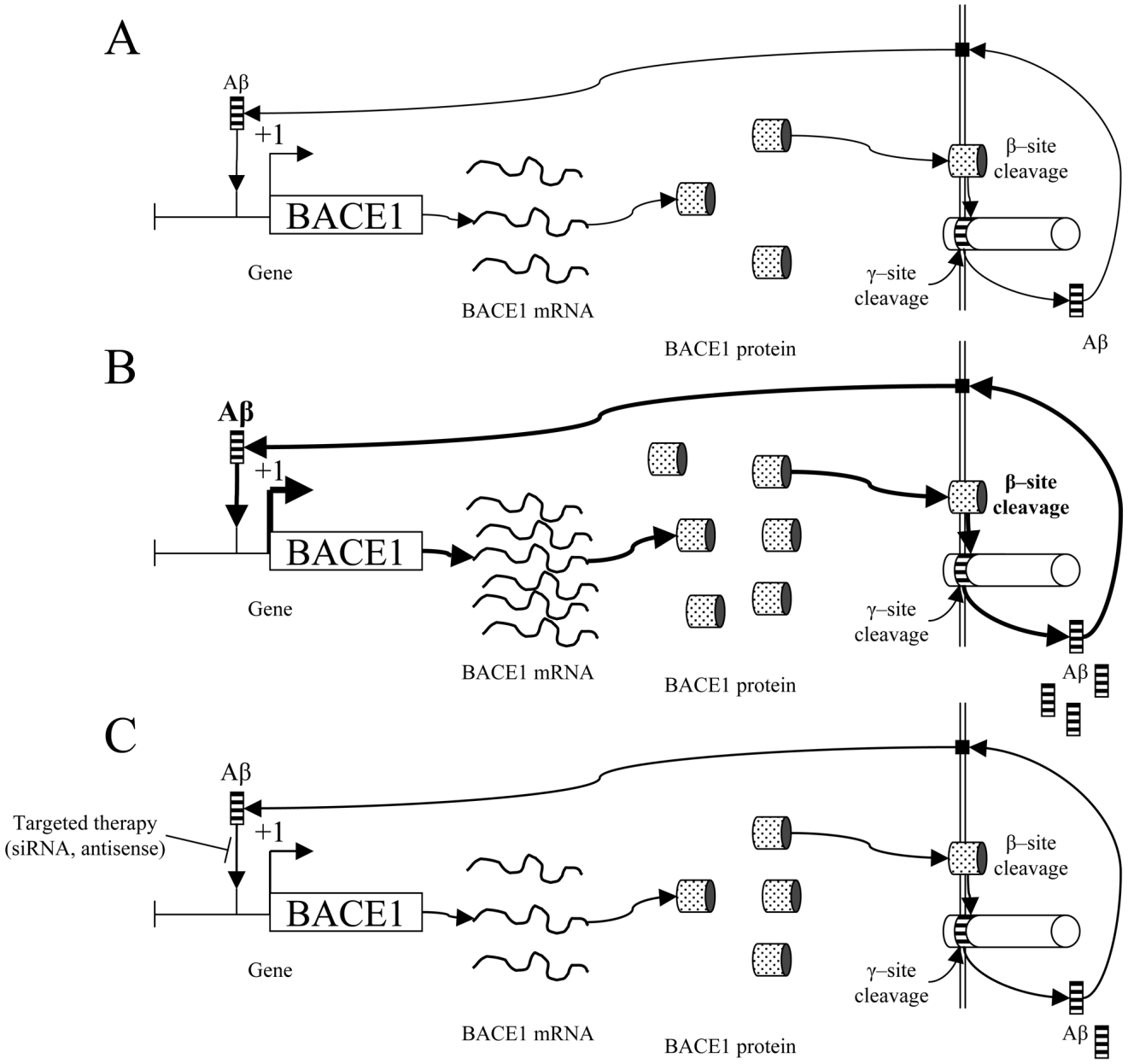

Fig. 1. Self–regulation of Aβ cleavage from AβPP through the BACE1 gene promoter and therapeutic implications

A) Intranuclear Aβ peptide would function as a transcription factor, upregulating BACE1 gene transcription. This would stimulate production of BACE1 mRNA as a template for BACE1 protein production. BACE1 would cleave AβPP at the β–cleavage site. When this is followed by γ–cleavage, extracellular Aβ is released. Aβ would then enter the cell through currently–uncharacterized receptor(s) that could include FPR2, insulin receptor, or NMDA receptors (Verdier, et al., 2004). Once within the cell, Aβ would then be transported into the nucleus to renew the cycle. B) Under pathogenic conditions, Aβ levels would have been stimulated to increase BACE1 transcription to the extent that normal Aβ clearance pathways, such as IDE, would fall behind. Additional Aβ would be transported into the cell, to stimulate increased BACE1 transcription, resulting in an uncontrolled positive feedback

loop. C) Therapeutic blockage of Aβ–BACE1 promoter interaction by sequence specific siRNA or antisense DNA oligomers would result in reduced BACE1 gene transcription, theoretically permitting Aβ clearance mechanisms to catch up to production. Reduced production would restore a state similar to pre disease levels.

Table 1

Clinical implications of candidate Aβ regulatory pathways

Pathway	Candidate Materials (examples only)	Comments
Kinase modification	Perifosine, Keryx (Gills and Dennis, 2009); CEP–1347, Cephalon (Wang and Johnson, 2008)	This pathway would allow use of drugs already developed. Potential for unexpected side effects due to wide activity profiles for target kinases; Low efficacy in clinical trials
Chelation	PBT2, Prana (Adlard, et al., 2008, Ritchie, et al., 2004)	Parent compound Clioquinol implicated in the disorder SMOM in large doses; PBT2 lower side effects
Cholesterol metabolism modification	Simvastatin, Merck (Tong, et al., 2009); D–4F, Novartis (Handattu, et al., 2009); Dietary modification (Pallebage-Gamarallage, et al., 2009)	Some agents already well–characterized for tolerability Dietary modification avoids drug therapy
Secretase modification	CTS–21166, CoMentis (Panza, et al., 2009); LY450139, Lilly (Bateman, et al., 2009); Etazolate, ExonHit (Marcade, et al., 2008)	Long–term effects of secretase modification unknown; Potential for interference in similar pathways (e.g., Notch vs. γ–secretase)
Aβ as a transcription factor	siRNA to Aβ–binding sites in target promoters; Antisense DNA to Aβ–binding sites in target promoters	Potential for high specificity (low side effects); Speculative; Little to no current clinical use