Special Focus: Molecular and Cellular Events Controlling Neuronal and Brain Function and Dysfunction

Neuronal protein trafficking associated with Alzheimer disease

From APP and BACE1 to glutamate receptors

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Aberrant and/or cumulative amyloid-beta (Aβ) production, resulting from proteolytic processing of the amyloid precursor protein (APP) by β and γ-secretases, have been postulated to be a main etiological basis of Alzheimer disease (AD). A number of proteins influence the subcellular trafficking itinerary of APP and the β-site APP-cleaving enzyme (BACE1) between the cell surface, endosomes and the trans-Golgi network (TGN). Available evidence suggests that co-residence of APP and BACE1 in the endosomal compartments promotes amyloidogenesis. Retrograde transport of APP out of the endosome to the TGN reduces Aβ production, while APP routed to and kept at the cell surface enhances its non-amyloidogenic, α-secretase-mediated processing. Changes in post-Golgi membrane trafficking in aging neurons that may influence APP processing is particularly relevant to late-onset, idiopathic AD. Dystrophic axons are key features of AD pathology, and impaired axonal transport could play crucial roles in the pathogenesis of idiopathic AD. Recent evidence has also indicated that Aβ-induced synaptic defects and memory impairment could be explained by a loss of both AMPA and NMDA receptors through endocytosis. Detail understanding of factors that influence these neuronal trafficking processes will open up novel therapeutic avenues for preventing or delaying the onset of symptomatic AD.

The Amyloid Cascade Hypothesis of Alzheimer Disease

An estimate 24.3 million people in the world have dementia in 2005.[1] With an extrapolated 4.6 million new cases of dementia every year, the number of dementia patient will double every 20 years, reaching 81.1 million by 2040. The neurodegenerative disease first reported by Alois Alzheimer[2] a hundred years ago[3,4] is the most common course of dementia in the elderly above 65 years. Alzheimer disease (AD), as it has become known, is therefore the

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neurodegenerative disease that has attracted the most research focus in the past decades.

Over 95% of AD cases are late-onset, sporadic and have a complex, idiopathic etiology. A small number of early-onset AD cases has hereditary monogenic defects, and investigations on the underlying mutations had provided important clues for understanding AD pathology. AD presents two distinct pathological features—intracellular neurofibrillary tangles (NFTs) and extracellular amyloid plaques. Both features have clear connections to neuronal demise and consequential onset of dementia symptoms. NFTs comprise of bundles of filaments twisted about each other in pairs (known as paired helical filaments, PHF), and contain abnormally hyperphosphorylated forms of the microtubule-binding protein tau.[5] Amyloid plaques are made up of insoluble aggregates of amyloid β (Aβ) peptides.[6,7] NFTs and amyloid plaques are functionally related, and the latter could potentially promote tau hyperphosphorylation and NFT pathogenesis.[8,9]

The amyloid cascade hypothesis[10] posits that accumulation of Aβ peptide, generated from proteolytic cleavages of the amyloid precursor protein (APP) in the brain, is the source of extracellular plaques, and the primary etiological agent of AD. However, extracellular amyloid plaque burden does not necessarily correlate with clinical AD symptoms, and it is known that Aβ exists in multiple assembly states, with each exhibiting different physiological or pathophysiological effects.[11-13] Accumulating evidence also suggests that both intracellular and extracellular soluble oligomeric forms of Aβ are capable of inducing synaptic defects and the onset of AD symptoms.[14-17]

As summarized in Figure 1, Aβ is generated from APP (but not its paralogues APLP1 and APLP2) by a sequential two-step proteolytic process involving β- and γ-secretases.[18,19] APP is first cleaved by the β-site APP cleaving enzyme 1 (BACE1),[20,21] a member of the pepsin family of aspartyl proteases, to generate a membrane bound C-terminal fragment (C99, CTFβ). A subsequent γ-secretase activity further generates peptides mainly of 40 or 42 amino acids in length, termed $A\beta_{40}$ and $A\beta_{42}$, as well as the remaining APP intracellular domain (AICD). Minor forms of Aβ peptides, including $A\beta_{35}$, $A\beta_{37}$, $A\beta_{38}$ and others with less clear neuropathological roles, can also be generated. $A\beta_{40}$ is more abundant than $A\beta_{42}$ and although both could be found in amyloid plaques, $A\beta_{42}$ is apparently more

directly neurotoxic,[22] and has a greater propensity to oligomerize and to form fibrils.[23] Interestingly, $A\beta_{40}$ appears to be able to reverse the above effect and properties of $A\beta_{42}$.[24-26] Alternative APP proteolytic processing pathways exist, most notably by α-secretases of the A Disintegrin and Metalloprotease (ADAM) family of surface metalloproteases.[27] α-secretase cleavage occurs at a site that effectively abolishes BACE1 recognition. The α-secretase cleaved C-terminal fragment (CTFα) is also subsequently cleaved by γ-secretase. However, the small fragment generated as such, named p3, is non-amyloidogenic and has no recognized role in AD. α-secretase cleavage also generates a soluble sAPPα fragment that has some neuroprotective properties.[28-31]

The γ-secretase[32] responsible for Aβ generation upon β-secretase-mediated cleavage of APP is not a single polypeptide. Rather, the proteolytic activity resides in a complex which mediates a unique process of regulated intramembrane proteolysis (RIP)[33-24] of several proteins, such as APP, Notch[35] and cadherin.[36] The active complex consists of at least four proteins—presenilins (PS)-1 or -2 at the catalytic core, nicastrin, anterior pharynx-defective phenotype 1 (APH1, two isoforms—APH1a and APH1b) and PS-enhancer 2 (PEN-2).[37-39] A fifth component, p23/TMP21, a member of the p24 cargo protein family, has recently been identified as part of the γ-secretase complex.[40] As alluded to above, γ-secretase cleavage also generates the AICD fragment, with possible transcriptional functions.[41,42] Other than cleavages by the conventional α, β- and γ-secretase, the intracellular domain of APP is also processed by caspases to a small 31-amino acid fragment that was shown to induce apoptosis.[43,44] APP is also cleave by the mitochondrial serine protease HtrA2, generating a C161 fragment (encompassing amino acids 535–695 of APP_{695}), which function is yet unclear.[45]

Known genetic predispositions[46,47] to early-onset AD are primarily associated with mutations in APP[48] and the presenilins 1/2 component of the γ-secretase complex.[49] All these mutations increase somewhat the generation of Aβ, or the $A\beta_{42}/A\beta_{40}$ ratio.[50,51] Endowment with the apolipoprotein E (ApoE) ε4 allele is a known risk factor for late-onset AD. ApoE ε4 appears to influence Aβ physiology in the aging brain in terms of its oligomerization and clearance, perhaps through its roles in lipid and cholesterol homeostasis.[52,53] On that note, there is evidence for high cholesterol levels in mid-life being a risk for AD[54,55] and preliminary evidence have suggested that cholesterol-lowering statins could reduce this risk.[56] The low density lipoprotein receptor (LDLR) family of proteins, which binds ApoE,
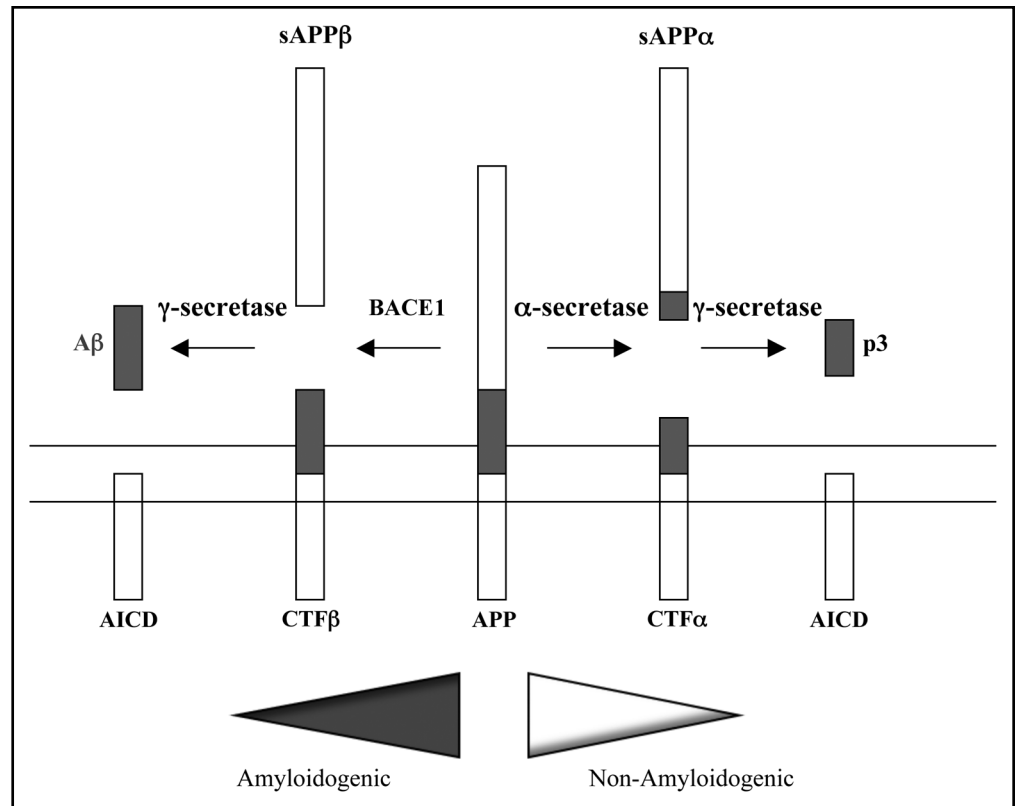

Figure 1. Proteolytic processing of APP. A schematic depiction of APP proteolytic processing. APP is a type I transmembrane protein. The Aβ peptide domain is located partially within the membrane spanning hydrophobic segment. In amyloidogenesis, the β-secretase recognition site is cleaved by BACE1 to a soluble fragment N-terminal fragment sAPPα, a C-terminal fragment CTFβ. The latter is then cleaved intramembranously by γ-secretase to yield Aβ and the APP intracellular domain (AICD). In the non-amyloidogenic pathway, α-secretases cleave at a site within the Aβ peptide sequence. This cleavage essentially disrupts the β-secretase recognition site. α-secretases cleavage yields the soluble N-terminal sAPPα, and the C-terminal CTFα. The latter can also be cleave by γ-secretase to yield a non-toxic 3 kDa fragment known as p3, and the APP intracellular domain (AICD).

modulates APP trafficking and proteolytic processing (see section 3 below). The neuronal sortilin related receptor 1 (SorL1, also named LR11 or SorLA) has in fact been recently found to be genetically associated with late-onset AD.[57] Several other potential genetic links to AD are known, including components of all three classes of the APP secretases, but not robustly confirmed. Excellent web information resources for these potential AD genes and loci could be found at www.alzforum.org.

APP interacts with multiple proteins, and these myriad of interacting partners could influence APP processing and AD pathology. Several diverse groups of molecules which superficially appear unrelated to AD pathology have also recently been shown to influence Aβ levels in vitro and in vivo through interactions with APP or the secretases.[58] These include the reticulon family members,[59,60] the Nogo-66 receptor,[61,62] the Rho family GTPases and their effectors,[63-65] as well as the peptidyl-prolyl isomerase Pin1.[66] Another important and interesting aspect of AD pathology concerns metals ions. Metal ions such as zinc and copper can interact with both APP and Aβ to potentiate AD by enhancing their aggregation as well as the generation of reactive oxygen species.[67-69] Oxidative stress has indeed been proposed to be a major mechanism for chronic neuronal death in AD.[70,71]

Neuronal membrane protein traffic, regulated or deregulated, plays vital roles in AD pathology. Although the etiology of AD appears complex, the pathological roots could be traced to Aβ generation from APP. APP and BACE1 have rather similar subcellular trafficking patterns and itineraries. Effective meeting and reaction between enzyme and substrate as they traverse the cell surface, endosome/lysosome, the trans-Golgi network (TGN) and the early secretory pathway would therefore determine the extent of Aβ production. Emerging evidence suggests that colocalization and interaction between APP and BACE1 in the endosomal compartments promotes amyloidogenesis. Retrograde transport of APP out of the endosome to the TGN reduces Aβ production, while APP routed to and kept at the cell surface enhances its non-amyloidogenic, α-secretase-mediated processing. Changes in post-Golgi membrane trafficking in aging neurons that may influence APP processing are therefore particularly relevant to late-onset, sporadic AD. Recent evidence also indicates that Aβ induced synaptic defects and memory impairment could be explained by loss of both the ionotropic glutamate receptors (AMPA and NMDA receptors) through localized dendritic spine endocytosis, involving fundamental mechanisms that are responsible for synaptic plasticity. This chapter focuses on how membrane traffic processes (and their defects thereof) may influence APP processing and Aβ production, as well as how Aβ could in turn cause synaptic defects by influencing the homeostatic trafficking of glutamate receptors.

Membrane Traffic Itinerary and Localization of APP, BACE1 and γ-secretase—Sites of APP Cleavage and Aβ Production

Both APP and BACE1 are type I membrane proteins with rather similar membrane traffic itineraries. Made at the cell body, they traverse both the exocytic and endocytic pathways of intracellular membrane traffic, and assume at least transient residence in various membrane compartments (summarized in Fig. 2). Productive interaction between APP and BACE1 resulting in β-secretase cleavage could potentially occur at multiple points in the ER, TGN, cell surface, endosome and lysosomes.[72,73] The γ-secretase complex, on the other hand, has a different mode of biogenesis (which includes functional subunit assembly) and membrane traffic dynamics from APP/BACE1. Identifying the predominant site (or sites) of β- and γ-secretase cleavages and consequential Aβ production has been controversial. The issues have been complicated by cell line and methodological differences, and the fact that localization or cleavage site may be altered as a result of mutations in the components concerned. Experimental overexpression of one component may also affect the trafficking of another. For example, high BACE1 expression could shift the subcellular location of APP cleavage to more proximal parts of the secretory pathway.[74]

β-secretase cleavage sites. β-secretase cleavage is the critical first step in amyloidogenic APP processing, and brain Aβ load correlated well with increased β-secretase activity in sporadic AD patients.[75,76] As BACE1 knockout mice appeared healthy,[86] BACE1 has emerged as a primed therapeutic target for AD.[77-79] Understanding BACE1 trafficking in relation to APP and APP cleavage is therefore important. Early studies have indicated that Aβ production involves the endocytic pathway,[80] and recent studies have strengthened the notion that endosomes are the principle sites of β-cleavage.[81] APP has at least two putative endocytic signaling motifs at its cytoplasmic

tail, and detail analysis by scanning mutagenesis indicated that the tetrapeptide sequence of YENP is the dominant signal for APP internalization.[82] Upregulation of the endocytic pathway stimulated by the endosomal Rab5 increased Aβ production,[83] while inhibition of dynamin-dependent endocytosis reduced it.[84]

The β-secretase activity has been known for some time, and the particularly sticky problem of investigating an enzyme activity without an identity was eventually resolved with the cloning of BACE1.[20] Mature BACE1 is found on the cell surface and endosomes, but not ER or lysosomes.[85] Sensitive fluorescence microscopy analysis by fluorescence resonance energy transfer (FRET) indicated that APP and BACE1 interact at the cell surface and endosomes, but not lysosomes.[86] Since biochemical studies indicate that BACE1 has an acidic pH optimum,[87] it follows that the acidic endosomes are the main compartments in which β-cleavage of APP occurs. This notion is further supported by the fact that cellular factors which influence APP and BACE1's trafficking in and out of endosomes also modulate Aβ production (see section 3 below).

γ-secretase cleavage sites. Attempts to identify the main γ-secretase cleavage site(s) have generated a good deal of controversy. Inhibition of γ-cleavage resulting from presenilin (PS)-1 knockout[88] and subsequent demonstration that it contains the catalytic site,[89] established it as an essential component of the γ-secretase activity. Unlike APP and BACE1, however, both PS1 and PS2 were localized to compartments of the early secretory pathway (ER and Golgi),[90] and there is evidence for "active" γ-secretase activity in a pre-Golgi compartment.[91] The exact localization of γ-secretase activity is also undoubtedly complicated by the fact that we are looking at a multi-protein complex that needs to be assembled[92,93] and also by the fact that active presenilin is itself an endoproteolyzed, membrane bound polypeptide. γ-secretase activity have been demonstrated in multiple cellular locations, even in the mitochondria.[94] More recent analysis is consistent with functional γ-secretase activity concentrating on the cell surface and in early endosomes.[95]

A potential function of presenilin that has not received as much attention as its catalytic activity is its role in protein trafficking,[96] in particular that of APP.[97] Surface APP transport is defective in cells overexpressing PS1 mutants which cause familial AD.[97] PS1 interacts with phospholipase D1 (PLD1).[98] Overexpression of PLD1 in wild type cells promotes generation of APP-containing vesicles from the TGN, corrects impaired neurite outgrowth in PS1 mutant neurons, and reduced Aβ generation.[99] Presenilin/γ-secretase activity is also apparently required for normal endosomal recycling of soluble and membrane-associated proteins, and treatment with γ-secretase inhibitors resulted in the accumulation of APP and APP-CTFs in the recycling endosome.[100]

Where is Aβ produced in the neurons? β cleavage versus α cleavage. Many cell types in the body express APP. In the brain, BACE1 expression is observed in most neurons. Glia cells expressed little or undetectable BACE1 under normal conditions, although activated astrocytes may have elevated BACE1 expression.[20,101] Neurons are therefore believed to be the major source of Aβ produced in the brain. Mature neurons are highly polarized cells with distinct axonal and somatodendritic plasma membrane domains. Endosomal compartments can be found in both axons and dendrite in isolation from those at the cell body. The dendrite is also endowed
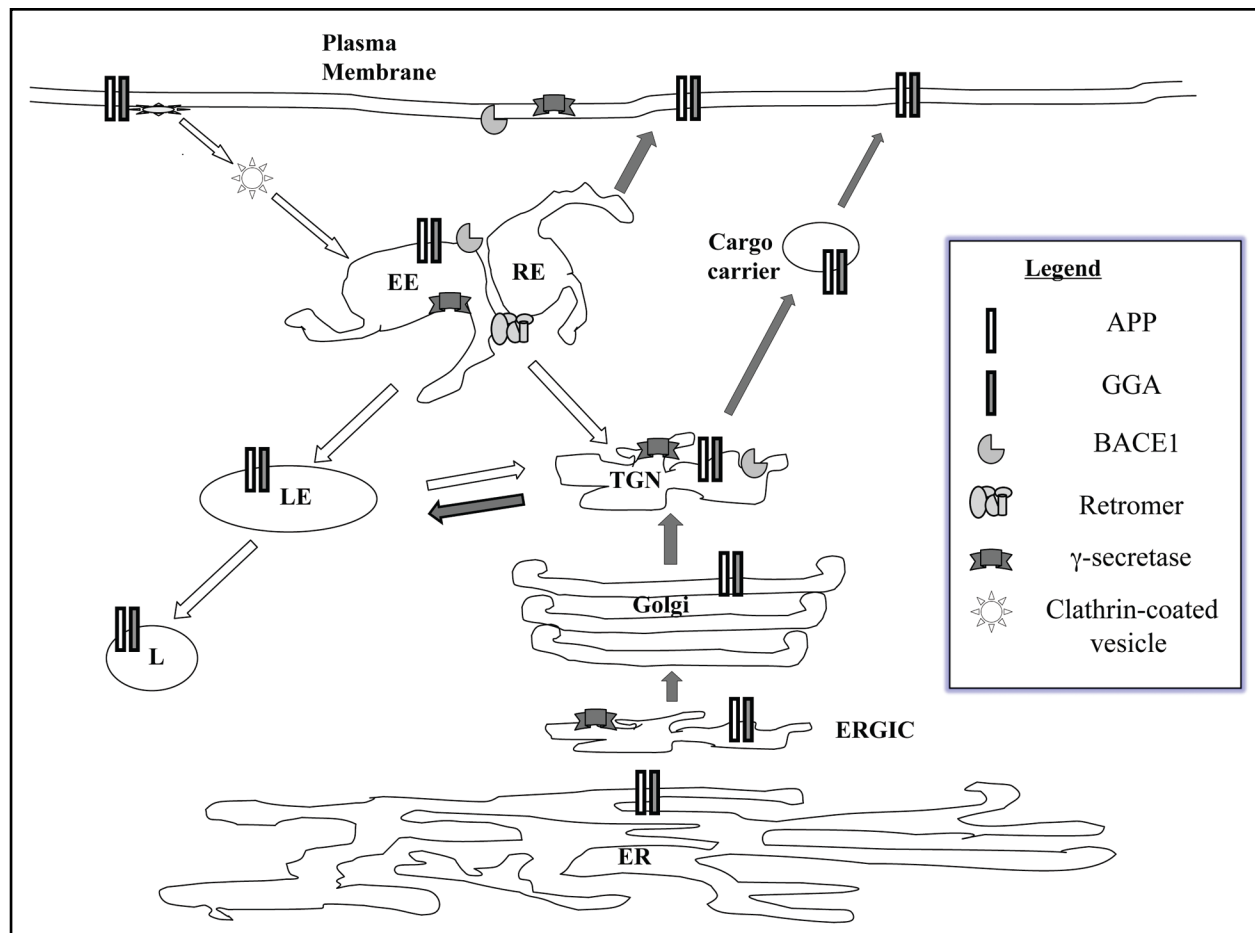
Figure 2. Trafficking itinerary of APP and BACE1. A schematic diagram of the trafficking itinerary of APP and BACE1. Both proteins have very similar itinerary and can be found in compartments of the exocytic pathway and endocytic pathway. Locations of general components of membrane traffic known to affect APP/BACE1 traffic, such as gamma-ear-containing ARF-binding (GGA) proteins and the retromer complex are also shown. Although presenilins are largely localized to the ER-Golgi region at steady state, these and other components of the γ-secretase complex also have widespread presence. Note that this is a general scheme which does not include detail depiction of neuronal domains such as axons and dendrites. Dark arrows indicate exocytic or anterograde transport and white arrow endocytic or retrograde trafficking. ER, endoplasmic reticulum; ERGIC, ER-Golgi intermediate compartment; TGN, trans-Golgi network; EE, early endosome; RE, recycling endosome; LE, late endosome; L, lysosome.

with rather elaborate internal membranes of the ER and Golgi.[102] In view of the highly polarized and complex traffic processes that occur in a neuron, it would be of considerable interest to know if there is a main site of Aβ generation, especially in connection with excess generation during AD pathology.

Another point of interest stems from the fact that proteolytic processing of APP by α-secretases would essentially preclude β-cleavage and Aβ generation[103] and Aβ generation is therefore influenced by APP's close encounters with either secretases in its trafficking itinerary. The plasma membrane was shown to be the major site for α-secretase cleavage of APP.[104,105] In polarized Madin-Darby canine kidney (MDCK) cells, APP is predominantly targeted to the basolateral membrane where α-secretases are found, but BACE1 is instead targeted to the apical membrane.[106,107] APP processing in MDCK cells therefore occurs mainly by α-cleavage.[107] In hippocampal neurons, BACE1 is mainly targeted to the axons[107] (analogous to the epithelial apical domain). On the other hand, APP has been shown in early studies to undergo axonal transport,[108] but could be transcytose to dendrites.[109] Recent work also suggests that APP can be transported in a non-signal dependent manner

to both axons and dendrites.[110] It appears that APP could be processed by both BACE1 and α-secretases on axonal plasma membranes. However, keeping in mind that BACE1 has an acidic pH optimum and is most active in endosomes, it would logically follow that axonal presynaptic endosomes may be a major site of Aβ production. This notion is supported by findings that endoproteolytic fragments of PS1 can be found in synaptic organelles and growth cone membranes,[111] but requires further experimental confirmation. In any case, it should be intuitively clear from the discussions above that the time spent by APP in the endosome versus that of other compartments (such as TGN and the plasma membrane) could have a major influence on Aβ production. Alterations in APP processing in favor of β-secretase cleavage resulting from changes in its trafficking dynamics and resident time in the endosomes, perhaps due to neuronal aging and cumulative oxidative damage, could therefore be relevant for late-onset, sporadic AD. This notion is explore further below as we look at how APP traffic and Aβ production is influenced by multiple cellular factors.

Factors Participating in or Influencing APP/BACE1/γ-Secretase Traffic and Aβ Production

A myriad of cellular factors and processes are known to influence APP/BACE1/γ-secretase traffic and consequential Aβ production. These include general molecular components of exocytic and endocytic traffic, as well as cargo adaptors that may specifically associate with APP. Their mode of function and interactions are briefly summarized below.

General protein trafficking components in APP/BACE1/γ-secretase traffic. Vesicular transport of APP and BACE1 is governed by the basic molecular machinery of protein traffic in eukaryotic cells. Both molecules are transported in their post-Golgi routes by clathrin-coated vesicles through its associated adaptor proteins. Polarized transport of APP in epithelial cells is mediated by the adaptor protein complex AP1-1B,[112] and a similar complex likely interacts with APP in neurons. APP, particularly the cytoplasmic NPXY motif, is known to interact with a host of molecules with implicated functions as cargo adaptors. Some of these molecules also interact with and regulate the trafficking of the ApoE receptor 2 (ApoER2). These are considered collectively in the following section. We first look at two known coat adaptor complexes that mediate BACE1 and APP traffic.

The cytoplasmic domain of BACE1 contains an acid cluster dileucine motif that binds the Vps-27, Hrs and STAM (VHS) domain of Golgi-localized gamma-ear-containing ARF-binding (GGA) proteins.[113] Overexpression of GGA1 in cells was reported to increase the level of APP C-terminal fragment (CTFβ) resulting from β cleavage but paradoxically reduced Aβ levels, which suggest that GGA1 somehow prevents CTFβ from being subjected to subsequent γ-secretase cleavage.[114] Another report, which showed that GGA1 is enriched in neurons of human brain, demonstrated that overexpression of GGA1, or a dominant-negative variant, reduced CTFβ generation and Aβ secretion.[115] On the other hand, silencing of GGA1 increased Aβ secretion. The general picture provided by these reports showed that GGAs have a pivotal influence on the cellular trafficking of BACE1 (and APP) between the TGN and the endosomal compartments, which in turn affects Aβ biogenesis. How GGA-mediated processes may change during AD pathology is still unclear. Interestingly, BACE1 levels appear to be regulated by that of GGA3. GGA3 protein levels were significantly decreased in AD brains, and this inversely correlated with increased levels of BACE1.[116]

Another coat complex implicated in the transport of BACE1 is the retromer complex, which has an evolutionarily conserved function in endosome-to-Golgi transport.[117] Retromer components are highly expressed in the brain, and silencing of the retromer component VPS26 incurred a change in BACE1 trafficking that was similar to GGA silencing.[118] Both VPS26 and VPS35 levels are reduced in brain regions selectively vulnerable to AD.[119] Like the GGAs, the retromer complex likely modulates BACE1 and APP partitioning between the endosome and the TGN. Although a role for the retromer complex in AD pathology is not supported by the lack of an association between its genetic polymorphism and AD risk,[120] changes in retromer subunit levels with age could contribute to late onset AD.

Other than coat proteins, the other two major classes of components of the mammalian protein traffic machinery, namely the Rabs and SNAREs, are less implicated in the modulation of APP or BACE1 traffic. Rab1B and Rab6, which regulates transport at the ER-Golgi boundary and the Golgi-TGN, respectively, appeared to influence APP processing.[121,122] One would also expect SNAP (soluble NSF attachment protein) and NSF (N-ethylmaleimide-sensitive factor) attachment receptors (SNAREs) operating at the TGN and endosomes of neurons[123] to participate in APP and BACE1 trafficking. Changes in the function and activities of these SNAREs should influence Aβ biogenesis, but have not yet been reported as such.

APP-interacting adaptor proteins influence APP trafficking and Aβ generation. Tyrosine phosphorylation of the YENPTY sorting motif at APP's C-terminus resulted in its interaction with several cytosolic phosphotyrosine binding (PTB) domain or Src homology 2 (SH2) domain-containing proteins.[124] Some of these, such as the munc-18 interacting proteins (Mints)/X11s, mammalian Disabled (DAB), the Fe65 family of proteins and the JNK-interacting proteins (JIPs), have been extensively implicated in the modulation of APP trafficking and Aβ production.[125] Almost invariably, these adaptors also influence trafficking of the ApoE receptor, ApoER2. It was recently shown that binding of ApoE to ApoER2 triggers the endocytosis of APP, BACE1, and ApoER2 in neuroblastoma cells, thereby increasing the production of Aβ. This is apparently mediated by X11α or X11β,[126] which bind both APP and the cytosolic domain of ApoER2.[127] Another report showed that X11γ/Mint3 and APP are found in the same purified transport vesicles. Silencing of X11γ enhanced endosomal/lysosomal sorting of APP and increased Aβ secretion.[128]

Mammalian disabled (mDAB)-1 likewise interacts with both APP and ApoER2, and decreased both CTFβ and secreted Aβ in a reelin-dependent manner.[129] Interestingly, X11α and mDab-1 exert opposing effects on APP processing, and when both proteins are co-expressed, the effect of X11α overrides that of mDab-1.[130] Fe65 is involved in APP signaling through the AICD[131] as well as several aspects of APP-processing, and it also binds ApoER2.[132,133] The JIPs are scaffold proteins that could link APP to JNK associated apoptotic functions[134,135] and kinesin that mediate APP (as well as ApoER2) axonal transport.[136] The interactions between APP and these binding proteins, and the resulting influences on APP trafficking and processing are exceedingly complex, and the links between APP and ApoER2 pertaining to AD pathology needs further clarification.

ApoER2 belongs to the family of LDL receptor-related (LRP) proteins, several of which have been implicated in APP processing and AD.[137-139] LRP1, a neuronal receptor for ApoE, binds to APP (either directly or through Fe65) affects Aβ generation and clearance in the brain. APP processing is mediated by LRP1 on multiple levels. Enhanced APP internalization through LRP expression decreased cell surface APP levels, thereby reducing APP-shedding and enhanced Aβ secretion.[140] In a recent report, LRP1 expression was shown to regulate ApoE and cholesterol levels within the CNS. Interestingly, deletion of APP, APLP2, or components of the γ-secretase complex, enhanced the expression and function of LRP1 in a way that is reversible by forced overexpression of AICD. The latter, together with Fe65 and Tip60, interacts with the LRP1 promoter and suppresses its transcription. The cellular interaction between APP and LRP1 thus goes beyond the physical interactions during protein trafficking, but occurs at the level of gene transcription as well. Several genetic polymorphisms of LRP1 have indeed been weakly associated with AD.

On the other hand, LRP1B, a homologue of LRP1, appears to retain APP at the cell surface and reduced Aβ production due to its slower rate of endocytosis.[141] Clearly, a detail understanding of LRP1 and LRP1B expression in AD-affected brain regions would be important, and may need to novel therapeutic approaches.

The neuronal sorting protein receptor-related containing LDLR class A repeats (SorLA) (also named SorL1 or LR11), is another neuronal sorting protein that plays pivotal roles in APP processing. SorLA has received much recent attention as a clear demonstration of genetic linkage of its variants to late-onset, sporadic AD has now been made,[66] consistent with earlier findings that its expression is reduced in brains of sporadic AD but not in familial AD cases.[142] SorLA interacts with both APP and BACE1, and its interaction with APP apparently reduced the latter's interaction with BACE1.[143] Overexpression of sorLA in neurons redistribution surface APP to the Golgi and decreased its processing to Aβ, whereas ablation of sorLA expression in knockout mice results in increased levels of Aβ in the brain.[143-145] SorLA may act to retain APP in TGN, and its sorting activity is dependent on functional interaction with adaptor proteins involved in protein transport to and from the trans-Golgi network, such as GGA and phosphoprotein acidic cluster sorting protein-1 (PACS-1).[146] SorLA is indeed an interesting and promising target for AD prevention or delay of late-onset AD symptoms. Recent findings with brain samples from antemortem diagnosis showed that SorLA levels are in fact already reduced in individuals with the pre-AD condition of mild cognitive impairment, and cognitive impairment is more severe for those with lower SorLA.[147] Another interesting report showed that docosahexaenoic acid feeding increases SorLA levels in multiple systems, including brain.[148] Dietary modulation of SorLA levels therefore provides a plausible explanation for the association of ω-3 fatty acids with improved cognition and reduced AD risk.

Other factors influencing APP trafficking and Aβ generation. New factors that modulate APP traffic continue to emerge. Genetic variants in the ubiquilin 1 (*UBQLN1*) gene, which encodes a ubiquitin-like protein on chromosome 9q22 increased the risk for AD, possibly through altered expression and alternative splicing in the brain.[149] Ubiquilin 1 knockdown seemed to increase the cellular maturation and trafficking of APP, enhancing the appearance of full-length APP on the cell surface. Secretion of sAPPα/β and Aβ40/42 were also increased.[150] Fluorescence resonance energy transfer (FRET) analysis demonstrated that APP and ubiquilin 1 do come into close contact in vivo. Another APP sorting signal interacting protein is PAT1, a microtubule binding protein.[151] PAT1 appears to modulate the trafficking of not just APP, but also its homologues APLP1 and APLP2.[152] Modulation of PAT1 levels by overexpression and siRNA-mediated silencing also changes APP surface expression and Aβ production.

Another factor that could modulate APP traffic is p23/TMP21, a member of the p24 family type I transmembrane proteins that was recently identified as a presenilin complex component capable of modulating γ-secretase cleavage.[40] TMP21 silencing increased secretion of sAPP and Aβ production. The effect of TMP21 depletion and expression of a familial AD-linked PS1 mutant on Aβ production appeared to be additive, and immunoisolation analyses showed a decrease in co-residence of APP and X11γ/Mint3.[153] Other than

modulating γ-secretase activity, TMP21 may therefore have a separate modulation effect on APP traffic.

All the findings discussed above provide a general picture of how modulation of trafficking of APP and its secretases by various cellular factors could modulate Aβ generation. Broadly speaking, enhanced retrograde transport of APP out of the endosome to the TGN reduces Aβ production. Enhanced APP routing to, or reduction of its internalization from the cell surface, facilitates its non-amyloidogenic, α-secretase-mediated processing. Changes in post-Golgi membrane trafficking in aging neurons that may influence APP processing may therefore precipitate late-onset, idiopathic AD.

Axonal Transport and Alzheimer Disease

Efficient and tightly regulated axonal transport from and to the neuronal cell body is essential for neuronal survival and function. Bidirectional transport of vesicles, organelles, cargo carriers and protein complexes occurs along specifically polarized microtubule tracks by engaging microtubule-dependent motor proteins of the kinesin and dynein superfamilies.[154] Impair axonal transport as a result of gene mutations is known to predispose individuals to pathogenesis of several neurodegenerative diseases.[155,156] Perhaps the most prominent of these are CNS motor neuron diseases such as amyotrophic lateral sclerosis (ALS).[157] Mutation in the dynactin subunit, p150*Glued*, for example, is a genetic risk factor for ALS.[158] In Huntington's disease, the mutant huntingtin protein has an expanded polyglutamine tract and impairs axonal trafficking in mammalian neurons in vivo and in vitro.[159] Certain forms of the peripheral neuropathy Charcot-Marie-Tooth type II could also result from mutations in traffic components such as the microtubule motor KIF1β,[160] regulator of vesicular traffic such as Rab7,[161] and neurofilament[162] that cause defects in axonal transport. There are many histopathological as well as cellular and molecular links between AD and defects in axonal transport, as elaborated in more detail below.

Impairment of axonal transport in AD. The two major pathological hallmark features of AD are amyloid plaques consisting of aggregated Aβ and neurofibrillary tangles (NFT) containing hyperphosphorylated tau. Another prominent histopathological manifestation of AD is the presence of abnormal and dystrophic axons and dendrites. These may be associated with amyloid plaques and NFTs,[163,164] but are in some cases found unassociated with either plaques or tangles.[165,166] Mouse models overexpressing wild type and mutant forms of AD-related proteins such as APP,[167] BACE1,[168] PS1,[169,170] tau[171,172] and ApoE4,[173] have all been shown to exhibit axonal defects as in human AD. Interestingly, co-expression of the Drosophila homologue of APP, APPL, together with tau, also disrupts axonal transport in flies.[174] Selective white matter changes indicative of axonopathy are readily detected by magnetic resonance imaging (MRI) of AD patients.[175,176] All the above indicate that AD pathogenesis causes axonal defects. That dystrophic axons could be found before clear plaque deposition or tangle formation in transgenic animals, and that white matter changes could be detected in pre-AD patients, would also suggest that axonal defects occurs rather early in AD pathogenesis.

How exactly does onset of AD pathology result in axonal defects? It is worth noting that many proteins associated with the pathogenesis of AD are transported to the axons and the presynaptic

compartment,[177,178] and that synaptic release of Aβ contributes significantly to extracellular amyloid deposits.[179] APP has been shown to undergo fast axonal transport[108] through direct binding with kinesin-1.[180] It was in fact suggested that BACE1 and PS-1 are also co-transported with APP in a membranous vesicular compartment, with the latter functioning like a membrane receptor for kinesin-1.[181] These earlier findings have recently been disputed,[182] but there is little doubt that axonal/presynaptic trafficking of APP and its processing enzymes occurs in normal and dystrophic neurons. Another point to note is that APP (and BACE1 and PS-1) are often found to accumulate in damaged axons following traumatic brain injury,[183,184] probably resulting from axolemmal disruption and impaired axonal transport.[185] Traumatic brain injury is a known epigenetic risk factor for AD,[186] and one plausible link could be aberrant production of neurotoxic Aβ with a detrimental positive feedback mechanism that further damages the surviving axons.

In understanding the basis of axonal transport defects in AD, a particularly relevant point to consider is the involvement of abnormally phosphorylated tau in AD pathology. Tau is an axonally transported microtubule-associated protein.[187] Hyperphosphorylation of tau not only results in a loss of function in terms of impaired microtubule binding, but probably also a toxic gain of function[188] that may disrupt axonal transport.[189,190] Tau is known to be involved in regulating axonal transport, and this notion is augmented by recent evidence showing that tau interacts with the dynactin complex.[191] Interestingly, in spite of the frequent presence of tau-associated NTFs in AD, no tau mutations have been identified for familial cases of AD.

The ontogenic relationships between amyloid plaques and NFTs have been enigmatic. Aβ may interact with tau, either directly or indirectly, resulting in the latter's hyperphosphorylation[192,193] and drives NFT formation.[8,194] Aβ may also induce proteosomal impairments that affect tau degradation, leading to its accumulation.[195] Aberrant activation of the tau-phosphorylating cyclin-dependent kinase 5 (Cdk5) has also been heavily implicated in AD pathogenesis.[196] Aβ and other neuronal stress factors could activate calpain, thereby enhancing Cdk5 activation. Conversely, the neuroprotective sAPPα generated by the non-amyloidogenic processing of APP, suppresses Cdk5 activation. Recent advances also suggest that activated p25/Cdk5 could induce the production and intraneuronal accumulation of Aβ in vivo, prior to any apparent tau or amyloid-associated neuropathology.[197] Aberrant Cdk5 activation could therefore lie upstream of amyloidogenic Aβ production, with the latter feeding forward to further activate Cdk5, as well as glycogen synthase kinase 3-β (GSK3-β), resulting in tau hyperphosphorylation at later stages.

Could aging and brain injury-related axonal transport defects play a causal role in AD pathogenesis? While it is clear that axonal defect is a key disease manifestation of AD and is responsible for its symptoms, could it also play a causal role in precipitating idiopathic AD? Available data indicate that axonal defects can be found in both pre-AD and AD brains, either in association or not in association with amyloid pathology. The latter, in particular, points to the possibility that axonal defects could coincide with the earliest stages of AD pathogenesis. Particularly strong evidence for axonal defects underlying AD pathogenesis has been presented by Goldstein and colleagues.[167] The authors showed that reducing kinesin-1 gene dosage by half in APP transgenic mice enhanced axonal defects,

Aβ generation and amyloid deposition. The latter likely resulted from increased APP amyloidogenic processing in transport retarded axons.[198]

Idiopathic, late-onset AD is an age-dependent disease, and is therefore expected to be influenced and precipitated by chronic cellular defects that accumulate as the individual ages. An example of such contributive factors to AD that has received popular attention is oxidative stress and related mitochondrial dysfunction.[199] The potential of cumulative focal blockages in axonal transport resulting from a myriad of factors such as physical trauma and neurochemical toxicity in initiating AD pathogenesis are difficult to assess, but are definitely plausible. Injury to axons causes the formation of axonal spheroids—focal swellings that likely result from block transport.[200] Speculatively, what could possibly happen is that the accumulation of stalled APP and its processing enzymes in these focal injuries, resulting in increased APP processing and Aβ generations, perhaps even in a way that favors amyloidogenic ratios of Aβ40/Aβ42. These, together with other factors associated with brain injury (such as neuroinflammation), triggers a cascade of events that might increase tau phosphorylation and NFT formation. The notion of chronic and cumulative axonal transport defects leading to AD pathogenesis is attractive, and is an avenue for potential therapeutic interventions. However, further understanding of the underlying processes involved in the transition from axonal defect to AD is needed.

Aβ-induced Synaptic Defects and Glutamate Receptor Trafficking

Dementia, which is generally preceded by memory deficits and a decline in cognitive functions, is the primary neurological defect associated with AD. The amyloid cascade hypothesis as it was originally proposed suggests that accumulation of fibrillar β-amyloid and their deposition as insoluble extracellular plaques underlies these neurological deficits. A major caveat for the above notion is that amyloid burden does not necessarily correlate well with clinical severity of AD. In some cases AD symptoms and neuronal loss could be traced to brain regions that are amyloid free. Furthermore, memory and cognitive function deficits could become obvious much earlier than plaques. An opposite notion in fact suggests that the insoluble amyloid deposits are sinks, rather than sources of Aβ toxicity. Recent findings have indicated that non-fibrillar, soluble oligomers of Aβ could cause cognitive deficits by impairing synaptic function.[12,13] Aβ oligomers could induce aberrations in synapse composition, shape and density, particularly in AD relevant excitatory pyramidal neurons.[201,202] Aβ oligomers may act presynaptically, suppressing spontaneous synaptic activity by inhibition of P/Q-type calcium currents,[203] or by disrupting synaptic vesicle endocytosis.[204] Soluble Aβ interacts with several receptor molecules, and have been postulated to disrupt synaptic memory mechanisms via stress-activated kinases and mediators of oxidative stress.[205] Excitatory transmissions could be depressed by both presynaptic and postsynaptic mechanisms.[206] A particularly relevant aspect Aβ's effect on synapses in AD is the impairment of hippocampal LTP.[207] It has in fact been shown that neuronal activity could modulate the formation and secretion of Aβ in hippocampal slices, with the peptide in turn depressing excitatory synaptic transmission.[208]

An important underlying mechanism by which Aβ suppress LTP (and presumably induce consequential memory impairment),

appears to be its influence on synaptic AMPA and NMDA receptors. AMPA receptors are the major excitatory neurotransmitter receptors in the brain, and its expression levels at the synapses are highly dynamic. Regulation of AMPA receptor to and from the synaptic plasma membrane, and localized recycling of AMPA receptors at dendritic spines are major mechanism underlying synaptic plasticity.[209,210] Aβ could interact directly with AMPA receptors and influence receptor function and channel activity,[211] and this may occur to varying degrees depending on Aβ levels. A more eminent mechanism by which Aβ induces synaptic depression involves enhanced loss of AMPA receptor from dendritic spine surfaces via endocytosis. Interestingly, this is mediated by signaling pathways similar to that occurring during long term depression (LTD), involving calcineurin and p38 MAP kinase activity.[212]

Aβ-induced depression of excitatory transmission and synaptic spine loss is dependent on NMDA receptor activity.[213,214] Although not perceived to be as dynamic as AMPA receptor, activity modulated alterations in NMDA receptor trafficking contributes to homeostatic plasticity.[215] Intriguingly, Aβ also promotes the endocytosis of NMDA receptors,[216,217] and does this via binding to α7 nicotinic acetylcholine receptor, initiating subsequent signaling processes that require calcineurin and the tyrosine phosphatase STEP (striatal-enriched phosphatase). Although Aβ's direct binding to α7 nicotinic acetylcholine receptor is a controversial issue,[218] Aβ treatment reduced surface NR2B and NR1, but not GABA receptor subunits.

Concluding Remarks

Advances in our basic understanding of biology are sometimes driven by intense efforts galvanized by the need to resolve a clinical problem. AD exemplifies such cases, as it is an exceptionally fascinating disease in terms of molecular and cellular etiology. Much of our understanding of the importance and mechanism of intramembrane proteolysis, for example, could be attributed to investigations on APP processing. In a similar way, studies on the subcellular trafficking and dynamics of the various membrane proteins associated with AD pathology are also pushing the frontiers of our understanding of protein trafficking in neurons. Much is now known, but there is much more to be learned. A detail understanding of factors that influence neuronal trafficking processes will open up novel therapeutic avenues for AD, as well as other neurodegenerative disorders.

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