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Dysregulation of Rab5-Mediated Endocytic Pathways in Alzheimer's Disease

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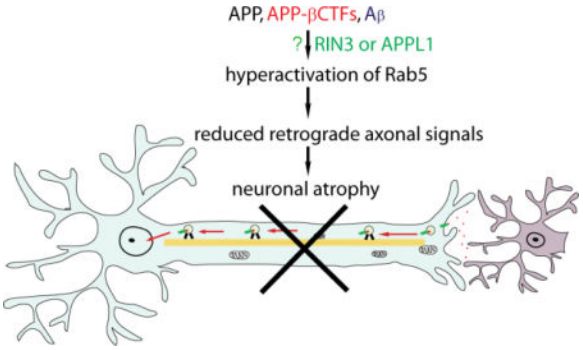
Abstract

Increasing evidence has pointed to that dysregulation of the endo-lysosomal system is an early cellular phenotype of pathogenesis for Alzheimer's disease (AD). Rab5, a small GTPase, plays a critical role in mediating these processes. Abnormal overactivation of Rab5 has been observed in post-mortem brain samples of Alzheimer's patients as well as brain samples of mouse models of AD. Recent genome-wide association studies of Alzheimer's disease have identified RIN3 (Ras and Rab Interactor 3) as a novel risk factor for the disease. RIN3 that functions as a guanine nucleotide exchange factor for Rab5 may serve as an important activator for Rab5 in AD pathogenesis. In the review, we present recent research highlights on the possible roles of dysregulation of Rab5-mediated endocytic pathways in contributing to early pathogenesis of Alzheimer's disease.

Graphical abstract



Keywords

Alzheimer's disease; Rab5; endocytosis; axonal transport; axonal dysfunction; atrophy; neurodegeneration

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Introduction

Genetic complexity of Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that often results in memory loss and cognitive impairment[1–9]. The classical neuropathological hallmarks for AD include: 1) Aβ-amyloid-containing neuritic plaques and 2) phosphorylated Tau-containing neurofibrillary tangles (NFT)[2,3,10,11]. The clinical phase of AD is also marked significantly by synaptic loss, selective neuronal death, neurotransmitter loss, and neuroinflammation[1,3,4,6,8,10,11]. At present, there are no disease-modifying treatments for this fatal illness. As of today, mutations in three genes: amyloid precursor protein (*APP*), presenilin *(PS)1* and *PS2*, have all been linked to early onset of AD (EOAD)[12–15], which only account for a very small number of AD cases. Extensive investigation of these mutations have helped to formulate the Aβ-amyloid hypothesis[1,16], positing that small Aβ-amyloid peptides ($A\beta_{40/42}$) underlie the pathogenesis of AD. This has led to many clinical trials that use approaches (inhibitors, antibodies etc.) to target and to reduce the buildup of toxic Aβ-amyloid peptides. Unfortunately, the anti-amyloid-based treatments have all failed in clinical trials thus far[17,18]. Similarly, intensive efforts have also been made to develop inhibitors to prevent aggregation of Tau-containing neurofibrillary tangles. However, these efforts have also failed in recent clinical trials[19]. Nevertheless, studies of these hereditary mutations in APP, PS1/2 have helped to gain a greater understanding of the molecular pathogenesis of AD.

One of the most important lessons we have learned from these failed clinical efforts is that the cause(s) for AD is far more complex than we originally anticipated[11]. For example, the incidence of late-onset AD (LOAD) accounts for the majority cases of AD and the cause(s) for LOAD is far from clear in comparison to that for EOAD. In 2009, apolipoprotein E *(APOE)* that plays an important role in lipid transport, Aβ trafficking, synaptic function, immune regulation, and intracellular signaling[20], was identified as an established risk factor for LOAD[21]. More recently, large scale genome-wide association studies (GWAS) and a meta-analysis have identified significant associations between LOAD with SNPs in ~20 additional loci including *CLU, CR1, PICALM, BIN1, ABCA7, MS4A4, EPHA1, CD2AP, CD33, INPP5D, MEF2C, HLA-DRB1/HLA-DRB5, NME8, ZCWPW1, PTK2B, SORL1, CELF1, SLC24A4/RIN3, FERMT2* and *CASS4*[22–27]. Identification of these additional risk factors highlights the extraordinary genetic complexity of AD.

Dysfunction for the endocytic pathways contributes to early AD pathogenesis

A significant number of the newly identified AD risk loci (PICALM, BIN1, EPHA1, CD2AP, MEF2C, PTK2B, SORL1 and RIN3) that encode products that function predominantly in endocytic trafficking[10]. For instance, PICALM (phosphatidylinositol binding clathrin assembly protein), whose expression is reduced in AD[28–30], plays a central role in internalization, trafficking and clearance of Aβ via the low density lipoprotein receptor related protein-1 and Rab proteins (Rab5, Rab11)[29,31,32]; Expression of the longest isoform of bridging integrator 1 (BIN1), an adaptor protein that functions in clathrin-mediated endocytosis and endocytic recycling, was significantly increased in the AD brains compared to age-matched controls[33,34]. Furthermore, BIN1 is significantly correlated with

the amount of pTau-containing NFT pathology[34] and has been implicated in modulating Tau-associated neuronal toxicity[34–36]. The sortilin-related receptor 1 (SORL1) regulates intracellular trafficking and processing of APP[37–40]. In the absence or reduced expression of SORL1, APP is released into late endosomal pathway, where it is subjected to both β- and γ-secretase cleavage, thus driving Aβ production[41,42]. Mutations in SORL1 have been associated with both EOAD and LOAD[43,44]. In addition, APOE and CLU (Clusterin) both influence Aβ-aggregation and receptor-mediated Aβ clearance by endocytosis[20,45,46]. Although each of these genes confers only an incremental risk to AD, together they may play a significant role in altering endocytic processes, such as internalization, endocytic trafficking and signaling, that ultimately contributes to molecular pathogenesis of LOAD[47].

Endocytic trafficking and amyloidogenic processing of APP

Neurons with the most extraordinary architecture have elaborate dendrites and axons, so it is not surprising that strong evidence has suggested that these early endocytic processes are dysregulated in AD[48–51] and in AD cases of people with Down syndrome[52]. For instance, amyloidogenic cleavage of APP to yield Aβ likely occurs predominantly in the intracellular compartments[53–58]. Under normal conditions, the early endosome, marked by Rab5, is a major site of APP processing by β-secretase (BACE1) to yield the β-cleavage C-terminal fragment (β-CTFs)[59–62], which is further processed in late endosomes or trans-Golgi network (TGN) to give rise to Aβ. Therefore, APP metabolism that produces toxic β-CTFs and Aβ is intimately regulated by the endocytic pathways[48–51,63–68]. Dysregulation of Rab5 can thus profoundly impact APP processing and Aβ production. In AD, abnormal enlargement of Rab5-positive early endosomes is not only characteristic, it is early; it was observed in non-demented individuals who were diagnosed postmortem as fulfilling the pathological diagnosis of sporadic AD[48]. Interestingly, endosomal pathology was detected in brain regions that were free of Aβ or pTau pathology[48,69], suggesting that early endosomal abnormalities precede not only the onset of dementia but also the emergence of plaques and tangles.

Axonal toxicity of APP β-CTFs and pTau

Although neuronal toxicities by β-CTF or C99 have been observed for quite some time[70–73], little is known about the underlying cellular mechanism(s). Recent evidence has pointed to a strong adverse impact of β-CTF on synaptic plasticity and neuronal function. The effect appears to be independent of Aβ, but is intimately linked to early cellular pathology in AD[55,60,73–80]. Intra-neuronal accumulation of excessive β-CTFs likely contributed to worsening cognitive function in AD patients in failed clinical trials of γ-secretase inhibitors[17,18,74,78,79]. We and others have recently demonstrated that excessive β-CTFs increased the level of activated Rab5, i.e. GTP-Rab5, impaired retrograde axonal delivery of endosomes or trophic factors that resulted in neuronal atrophy[79–81].

Moreover, a recent study has demonstrated that pathogenic tau species, phorsphorylated tau (pTau) is also impacted by endocytic trafficking and by APP processing[82]. Using human-stem-cell-derived forebrain neurons, Moore and colleagues have shown that APP mutations and increased gene dosage of APP caused marked increase in both total Tau and phosphorylated Tau in these AD neurons[82]. They further demonstrated that γ-secretase

inhibition that resulted in accumulation of APP- β-CTF/α-CTF led to an increase in tau, while treatment with inhibitors of β-secretase decreased Tau[82]. Therefore, intracellular trafficking and processing of APP impacts tau proteostasis as well. Since disruption of tau homeostasis has been implicated in disrupting axonal function[19,35,36,83–87], the link between β-CTF and Rab5 dysregulation, and between endosomal dysfunction and pTau thus warrants further investigation. RIN3, the Ras and Rab interactor 3, a stimulator and stabilizer for GTP-Rab5[88,89] identified in recent GWAS studies[22,24,25], may fill an important gap linking β-CTF to Rab5 dysregulation in AD.

Dysregulation of Rab5 in Alzheimer's disease

Rab5 is a small GTPase that cycles between an inactivate GDP-bound form and an active GTP-bound form for its biological functions[90–94]. Activation of Rab5 requires guanine-nucleotide exchange factors (GEFs) such as RIN3[90,94]. Inactivation of Rab5 is under the control of GTP-hydrolysis-activating proteins (GAPs)[95] due to a low intrinsic rate of GTP hydrolysis by Rab5 itself. It is under the dual control by both GEFs and GAPs, and Rab5 regulates early steps of endocytosis, ensuing endosomal membrane trafficking, sorting and endosomal fusion[90–92,94,96].

Through interaction with numerous effectors such as: APPL1/2 [adaptor protein containing pleckstrin homology (PH) domain, phosphotyrosine binding (PTB) domain and leucine zipper motif 1][97], Rabaptin-5/Rabex-5, early endosome antigen 1 (EEA1), phosphatidylinositol 3-kinases[98–102], Rab5 contributes importantly to cellular homeostasis. These effector proteins specifically bind to the activated form of Rab5, i.e. the GTP-bound form (GTP-Rab5) and regulates tethering and fusion of the early endosomes[99,103–106]. Therefore, Rab5 plays a critical role in docking of endosomal membranes, and motility of endosomes and intracellular signal transduction[91,92,107].

Sustained activation of Rab5 will result its interaction with the class C VPS/HOPS complex, an established GEF for Rab7[108] residing on late endosomes, thus leading to conversion from $Rab5^+$ early endosomes to $Rab7^+$-late endosomes for degradation. Therefore, the timing and duration of Rab5 in GTP-bound form is tightly regulated to ensure a smooth transition from early to late endosomes. This is especially important for axonal neurotrophic signals. Extensive studies have demonstrated that neurotrophic factors such as nerve growth factor (NGF) binds to their Trk receptor to be internalized into $Rab5^+$ signaling endosomes that carry important downstream signaling machineries such as Erk, PI3K, PLCγ for axonal transport to deliver the trophic signals to the soma and nucleus[109–114]. An intriguing question is how the signaling endosome is retained as $Rab5^+$ early endosomes, but not progress to $Rab7^+$ late endosomes, during their transit within the long axons. Work from the laboratory of Dr. G. Li has shed lights into the potential mechanisms[115]. As it turns out, following activation by NGF, TrkA recruits a Rab5-GAP to quickly convert GTP-Rab5 to GDP-Rab5 to keep the level of GTP-Rab5 in check, thus preventing the Rab5 to Rab7 conversion. As a result, the NGF/TrkA signaling endosomes is prohibited from premature degradation[115].

Given the important roles played by Rab5 in retrograde endosomal sorting and trafficking, it is not surprising that recent studies have demonstrated that the function and activity of Rab5

is compromised in early phases of Alzheimer's disease[49,50,64,80,81,92,93,116], as well as in mouse models of Parkinson's disease[117,118]. Persistent hyperactivation of Rab5 upsets other endocytic pathways such as late endosomes, lysosomes and autophagy, processes that have all been found to be altered in AD[48,51,63,119,120]. An important consequence of these changes under the pathological condition results in premature degradation of the neurotrophic factor signaling, thus effectively preventing the delivery of retrograde trophic signals to the soma/nucleus, leading to neuronal atrophy. This is indeed the case for early degeneration of basal forebrain cholinergic neurons in Down syndrome[111,113].

Dysfunction of retromers has also been implicated in AD[62,121,122]. Retromer is a protein complex that mediates endosome-to-Golgi transport. The levels of Vps35 and Vps26, two key retromer proteins, were significantly reduced in the entorhinal cortex of AD patients[62,121]. Vps26 binds to a hexapeptide motif (FANSHY) in the cytoplasmic tail of the sorting receptor SorLA (aka SORL1 or LR11)[123,124]. SorLA is a neuronal sorting protein that directs trafficking of APP also from endosomes to the Golgi[123,124]. It is thus conceivable that reduced levels of SorLA in conjunction with dysfunctional retromer would exacerbate the deficit of APP trafficking from endosomes to Golgi, resulting in accumulation of APP in endosomes. It is within the endosomal compartments enriched with proteolytic enzymes, APP is processed by β-secretase to drive production of β-CTF and Aβ[62,122–124].

In addition to Rab5 containing-early endosomes, the recycling endosomal pathways mediated by Rab4/Rab11 that regulate intracellular sorting, trafficking and processing of APP has been found to be altered as well in AD[125]. Accumulation of APP β-CTF has been shown to impair a key neuronal specific soma-to-axon transcytosis pathway[126,127]. Using induced pluripotent stem cell (iPSC)-derived human neurons with familiar AD mutations in PS1 (presenilin 1) and APP, a recent study from Dr. L. Goldstein's laboratory has demonstrated that subcellular distribution and trafficking of APP was altered in these neurons[126]; the level of APP was increased in the soma while APP in the axons was significantly reduced, a pattern closely reminiscent the distribution of Rab11 in these neurons[126]. Furthermore, knocking down Rab11 induced a similar defect in soma-to-axon transcytosis of APP in isogenic control neurons[126]. These studies have demonstrated that Rab11 plays a key role in the neuronal soma-to-axon transcytosis and dysfunction of Rab11 may also contribute to the early phase of AD pathogenesis.

Increased APP and its β-CTF leads to enlargement of Rab5+ early endosomes

One of the earliest neuronal pathologies of AD is endosomal dysfunction, that was observed in AD patients prior to the deposition of any extracellular β-amyloid (Aβ)[128–130]. In addition, patients with Down Syndrome (DS), who are known to develop AD pathology after the age of 40, also show these same endosomal abnormalities as early as 28 weeks of gestation[111,128]. These findings suggest that neurons become compromised intracellularly well before any plaque formation or tau accumulation occurs in the brain. Endosomal alterations reported in these two neurological disorders include increased endocytosis and enlarged early endosomes that contain the early endosomal protein Rab5[129–132]. Studies have also provided evidence that the cellular level of amyloid precursor protein (APP) is

linked to Rab5 containing early endosomal abnormalities[111,128–132]. APP, which is triplicated in DS and is one of the main proteins implicated in AD, is a transmembrane protein which is cleaved first by β- or α-secretase producing the corresponding APP C-terminal fragments: β-CTF or α-CTF. Cleavage by γ-secretase then produces the APP intracellular domain (AICD) and generates the Aβ peptides. Of these, several APP gene products and processed fragments, the full-length APP and β-CTF, have been shown to play a direct role in the early endosomal pathologies seen in AD and DS[110,128,131,132]. Recently, we shown that excessive full-length APP, APP mutants and APP β-CTFs, but not APP α-CTFs or AICD, could elevate the Rab5 activity and induce the enlargement of early endosome in both PC12M cell and primary basal forebrain cholinergic neurons (BFCNs)[80], which degenerates early in AD[113,133–138]. Importantly, APP β-CTFs induced neuronal atrophy in cultured rat E18 BFCNs and these effects by APP β-CTFs were rescued by a dominant-negative Rab5 mutant in vitro in cultured BFCNs as well as in a fly model of AD[80]. Therefore, consistent with studies from Dr. Nixon's group[81], these studies have demonstrated a role played by APP β-CTFs in mediating cellular toxicity by accumulation of toxic APP products.

APP/β-CTF acts through Rab5 to impair retrograde axonal trafficking of nerve growth factor leading to neuronal atrophy

NGF is a target-derived neurotrophic factor that acts through its surface TrkA receptor to support the survival, differentiation, and maintenance of BFCNs[139,140]. NGF signaling regulates expression of genes and cellular programs important for the BFCN phenotype, including cell size[113,140]. Following endocytosis, the NGF/TrkA signaling complexes are trafficked to $Rab5^+$ early endosomes[109,114]. The "signaling endosomes", as depicted in Figure 1, are then transported in a retrograde direction to the corresponding cell bodies to transmit NGF trophic signals[139,140]. Thus, axonal trafficking mediated by $Rab5^+$ early endosomes plays a critical role in maintaining the trophic status of BFCNs. Any alteration in these aspects could potentially disrupt axonal transport, resulting in neurodegenerative disorders. Recently, our group together with Dr. Nixon's laboratory found that APP β-CTF act though increased activation of Rab5 to cause enlargement of early endosomes[79–81]. Consequently, retrograde axonal trafficking and signaling of NGF in BFCNs or brain-derived neurotrophic factor in cortical neurons is reduced through increasing pauses[79,80]. Importantly, disruption of retrograde axonal trafficking of NGF signals results in trophic deficits in BFCNs, leading to neuronal atrophy[80]. Importantly, we have demonstrated that axonal transport deficits and neuronal atrophy can be rescued through the expression of a dominant negative Rab5 mutant, both in BFCN neurons as well as in a fly model of AD[80]. These studies have further confirmed the contribution of hyperactivated Rab5 to axonal transport deficits and neuronal atrophy in AD[79–81].

Based on our studies, we propose the following model to explain how NGF-TrkA signaling transport is impacted in the presence of APP β-CTF through increased activation of Rab5. In normal BFCNs (Figure 2A), NGF binds to and activates TrkA at the axonal terminals. The NGF-TrkA signaling complex undergoes endocytosis and is internalized into the cell cytoplasm to form $Rab5^+$ signaling endosomes. The signaling endosomes are transported in a retrograde direction along the microtubule toward the cell body to propagate the growth

and differentiation signals to the nucleus. The NGF/TrkA machinery is then attenuated in the cell body in late endosomes and lysosomes.

However, under pathogenic conditions, BFCNs are loaded with excessive APP and APP β-CTF (Figure 2B), which in turn results in an increase in the level of GTP-Rab5 leading to sustained activation of Rab5. Overactivation of Rab5 induces the enlargement of early endosomes that impair endocytic trafficking of APP, further exacerbating its processing. In addition, abnormally enlarged early endosomes may interfere with retrograde axonal transport of NGF signals. Additionally, increased Rab5 activity may also impact motor proteins to impair axonal transport. The net effect of all these aspects of APP and APP β-CTF will be reduced trophic signals being delivered to the soma, which will lead to neuronal atrophy[111,113].

The missing link between APP/β-CTF and Rab5 activation

1: RIN3—Recent GWAS studies have identified RIN3 as a risk factor for AD. RIN3, a guanidine nucleotide exchange factor (GEF) for selective members of the Rab5 family (Rab5, Rab21, Rab22, Rab24 and Rab31)[88,89], functions as the stimulator and stabilizer for GTP-Rab5[88,89]. RIN3 has a Src homology 2 (SH2) domain, a proline rich domain (PRD), a RIN-homology (RH) domain, a Vps9 (vacuolar protein sorting-associated protein 9) conserved in the catalytic domains of the Rab5 GEFs (Vps9p, Rabex-5 etc.) and a Ras-association (RA) domain (Figure 3A)[88]. It is possible that increased activity of RIN3 is responsible for the increase in the level of GTP-Rab5, that results in early endosomal abnormalities and axonopathy, leading to neuronal degeneration in AD. However, it remains to be defined: 1) if and how the function and expression of RIN3 is altered in AD; 2) if and how the activity of RIN3 is impacted by APP and APP β-CTF that results in hyperactivation of Rab5; and 3) whether or not Rab5 GEFs other than RIN3 also play a role in increased Rab5 activation in AD.

2. APPL1—In addition to RIN3, APPL1 (adaptor protein, phosphotyrosine interacting with pleckstrin homology domain and leucine zipper 1), an Rab5 effector (Figure 3B), has been shown to link APP β-CTF to Rab5 overactivation in AD and Down syndrome[81]. In a recent study, Dr. Nixon's laboratory has elegantly demonstrated that both APPL1 and β-CTF are increased in AD and that β-CTF binds to the YENPTY domain to the PTB domain of APPL1 and recruits APPL1 to Rab5 endosomes[81]. They have demonstrated that the increased presence of APPL1 to Rab5 endosomes leads to stabilization of active GTP-Rab5, which contributes to endocytic dysfunction e.g. pathologically accelerated endocytosis, abnormal enlargement of endosomes and impaired axonal transport of Rab5 endosomes[81]. Importantly, these endocytic defects in fibroblasts from Down syndrome were rescued by knocking down APPL1. Therefore, APPL1 represents an important adaptor that links APP β-CTF to hyperactivation of Rab5 and to endosomal dysfunction in AD and Down syndrome. However, this novel APPL1-dependent pathogenic pathway in AD will need to be further validated.

Dysregulation of Rab5 in Parkinson's disease

In addition to AD, recent studies have also pointed to that Rab5-mediated endocytic functions are impacted in Parkinson's disease (PD), for which α-synuclein aggregates, a major component of Lewy bodies (LBs) and associated Lewy neurites (LNs)[141,142], play a central role in the pathogenesis of the disease. The presence of α-synuclein aggregates significantly impacts intracellular vesicular trafficking by Rab proteins[58,143]. Conversely, these Rab proteins appear to modulate the protein level, aggregation, spreading and also toxicity of α-synuclein[143]. For example, Rab5A-mediated endocytosis of α-synuclein was found to be correlated with the neuronal cell death and with the that subsequently caused the formation of Lewy body-like intracytoplasmic inclusions[144]. Importantly, expression of a GTPase-deficient Rab5A mutant reduced endocytosis of α-synuclein and abrogated its cytotoxicity[144]. Using an APP transgenic mouse model of Alzheimer's disease, a recent study found that reducing endogenous α-synuclein restored the levels of Rab3a and Rab5 proteins[58]. In our recent study, we have observed increased expression of α-synuclein interacts with dynein motor and induces endosomal dysfunction by enhancing the level of activated Rab proteins (Rab5, Rab7), and hyperactivated Rab5 in a PD mouse model overexpressing wildtype α-synuclein. And all this may contribute to the impairment of retrograde axonal transport of BDNF and neuronal atrophy[145].

Possible interplays between Rab5 activation and PICALM, BIN1 in AD pathogenesis

Increasing evidence has pointed to the disturbance of Rab5-mediated endocytic pathways possibly playing a critical role in early cellular pathogenesis of AD and other neurodegenerative disorders such as PD. It remains unclear how these Rab5-mediated pathways interact with the GWAS hits (PICALM, BIN1, CD2AP, EPHA1, and SORL1), that also function at various stages of endocytosis[10,11], to impact pathogenesis in LOAD. We have just begun to understand how these GWAS hits impact endocytic pathways, potentially leading to neurodegeneration in AD. For example, PICALM[28,29,31,32] and BIN1[34–36] both function in clathrin-mediated endocytosis. Yet, the level of PICALM was reduced in LOAD patients[10,11], while BIN1 expression was increased in the brain of AD patients who carry high-risk polymorphisms upstream of BIN1[35,45]. Although PICALM has been suggested to promote APP processing and increase Aβ production in neurons, it is possible that PICALM plays a more important role in Aβ clearance from the brain by facilitating internalization of Aβ into endothelial cells and consequently releasing it to the bloodstream[146]. Since expression of PICALM is much higher in endothelial cells than in neurons[147], reduced levels of PICALM may therefore impair Aβ clearance more that Aβ production in LOAD patients. Increased accumulation of extracellular Aβ will undoubtedly upset the Rab5 endocytic pathways in neurons to impact their well-being[52]. This may explain why a minor PICALM allele (rs3851179 SNP), associated with increased expression of PICALM, is protective against AD likely by increasing clearance of extracellular Aβ to reduce its toxicity on neurons[28]. On the other hand, although the pathogenic mechanism of BIN1 is presently unknown, one can speculate that elevated level of BIN1 in LOAD patients[34–36,45] increase endocytosis and promote Aβ production in neurons[35], which in turn may induce activation of Rab5 to impair trafficking and signaling of neurotrophic factors[52].

Conclusion

AD is an extremely complex disease that involves many different cell types, factors and pathways. These different components may act independently or work in tandem to contribute AD pathogenesis. It has become increasingly clear that homeostasis of endocytic sorting, trafficking and signaling, that is critical for maintaining neuronal function, is disrupted in AD. Those AD risk factors discovered in GWAS studies that target the endocytic pathways may act alone or work in tandem to impair the normal function and process of the endocytic pathways. Delineating the interplays among these factors and pathways will not only enhance our understanding of the mechanisms responsible for neurodegeneration in AD and other diseases, but also will facilitate the discovery of novel target for developing treatment strategies for these disorders.

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A brief synopsis statement

Dysregulation of the endo-lysosomal system has emerged as one of the early cellular pathologies for Alzheimer's disease (AD). Rab5 is a small GTPase that plays a critical role in mediating internalization and endocytic trafficking. Recent studies have demonstrated Rab5 is hyper-activated and $Rab5^{+}$ early endosomes are found to be abnormally enlarged in post-mortem brain of AD patients and in mouse models of AD. In the review, we will summarize recent research findings linking Rab5 dysfunction to AD pathogenesis.

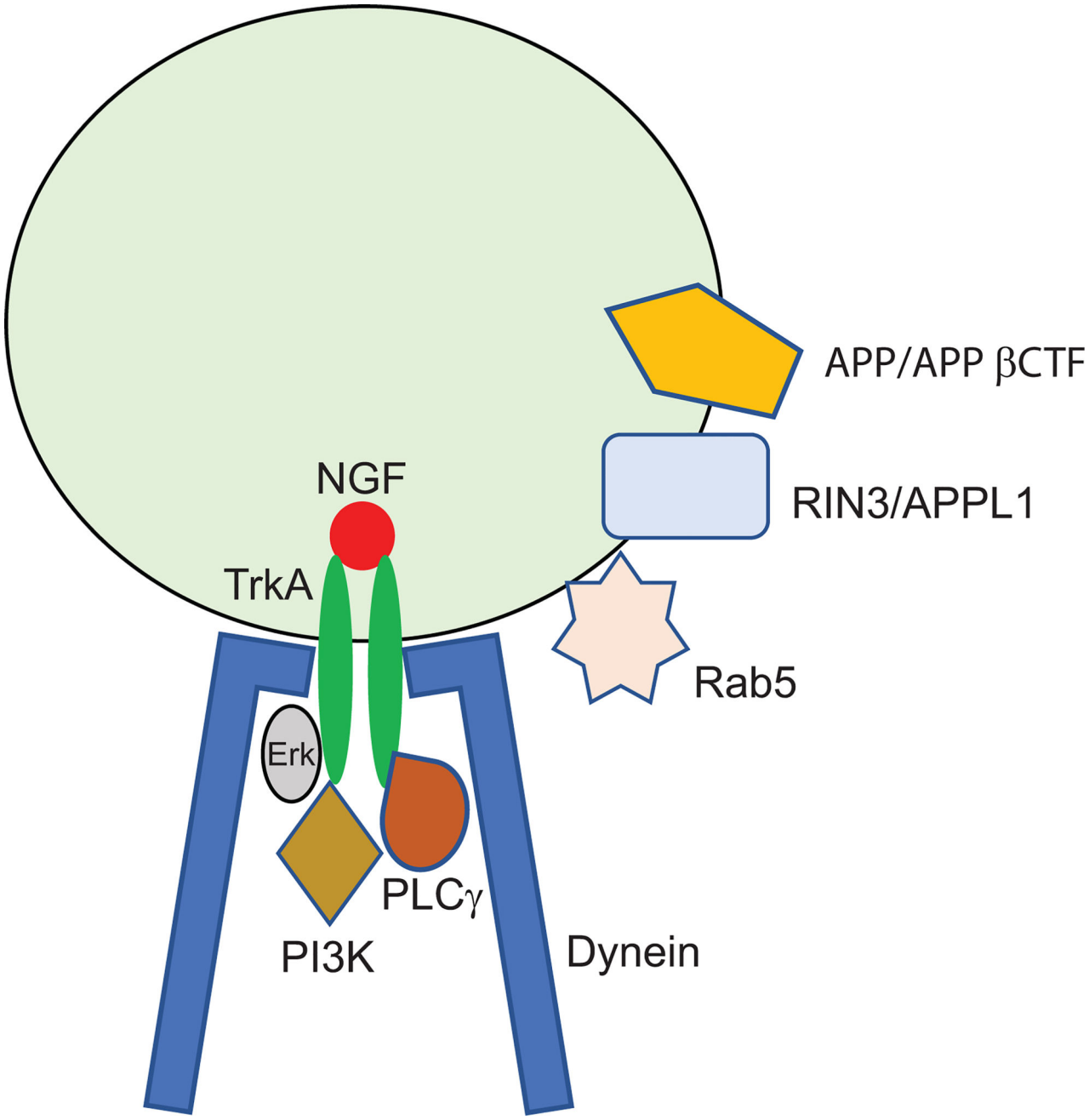

Figure 1.

A simplified depiction of an NGF signaling endosome showing that NGF binds to TrkA that activates the Erk, PI3K and PLCγ signaling cascades. In addition, APP/APP βCTF may act through RIN3 or APPL1 to activate Rab5. The dynein motor protein complex is also required to drive the retrograde axonal transport of the NGF signaling endosome.

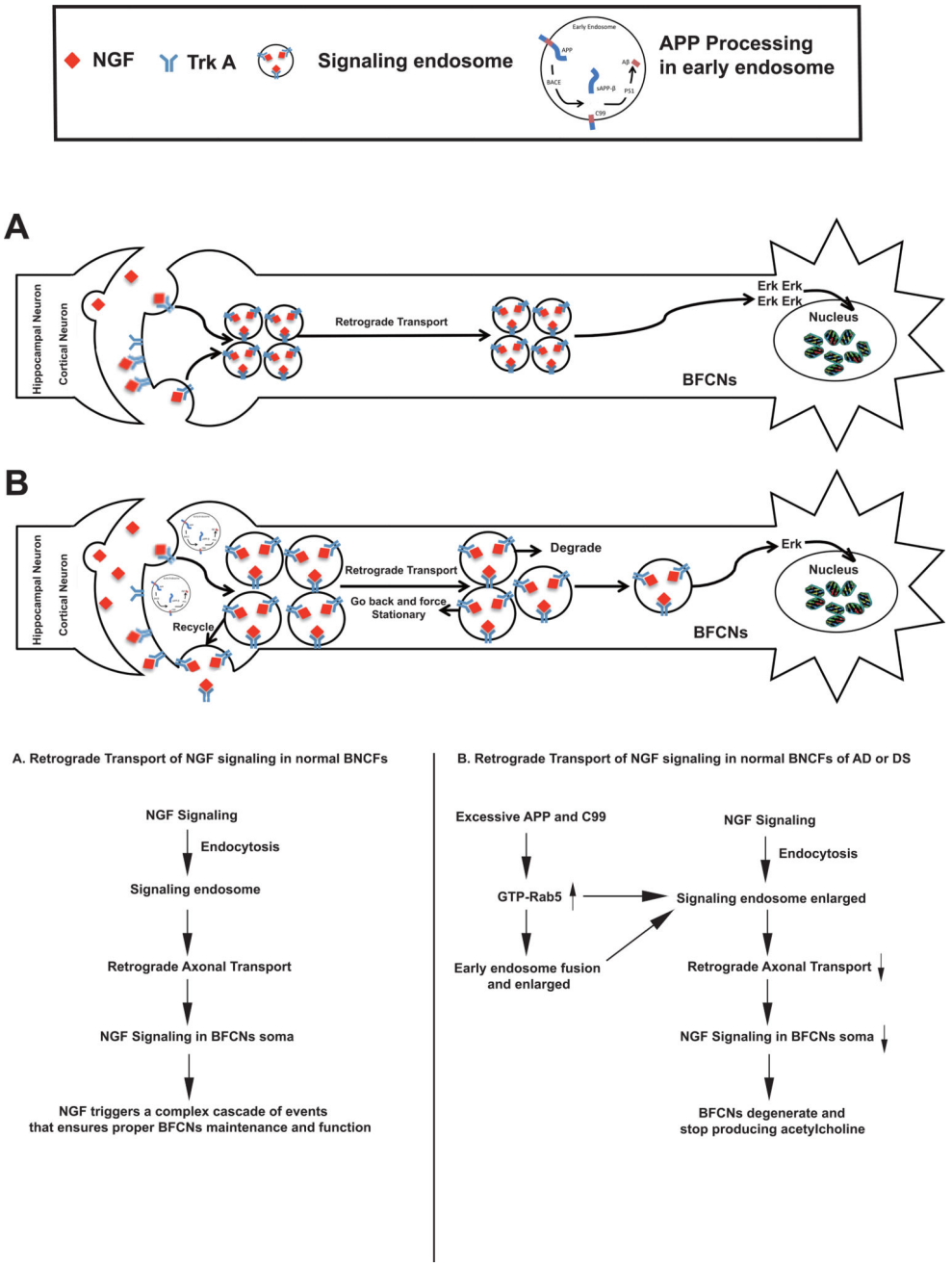

Figure 2.

Proposed models for retrograde axonal transport function of NGF signaling endosomes in normal neurons (A) and under conditions of excess APP or APP βCTF (B). Please see the text for a detailed description.

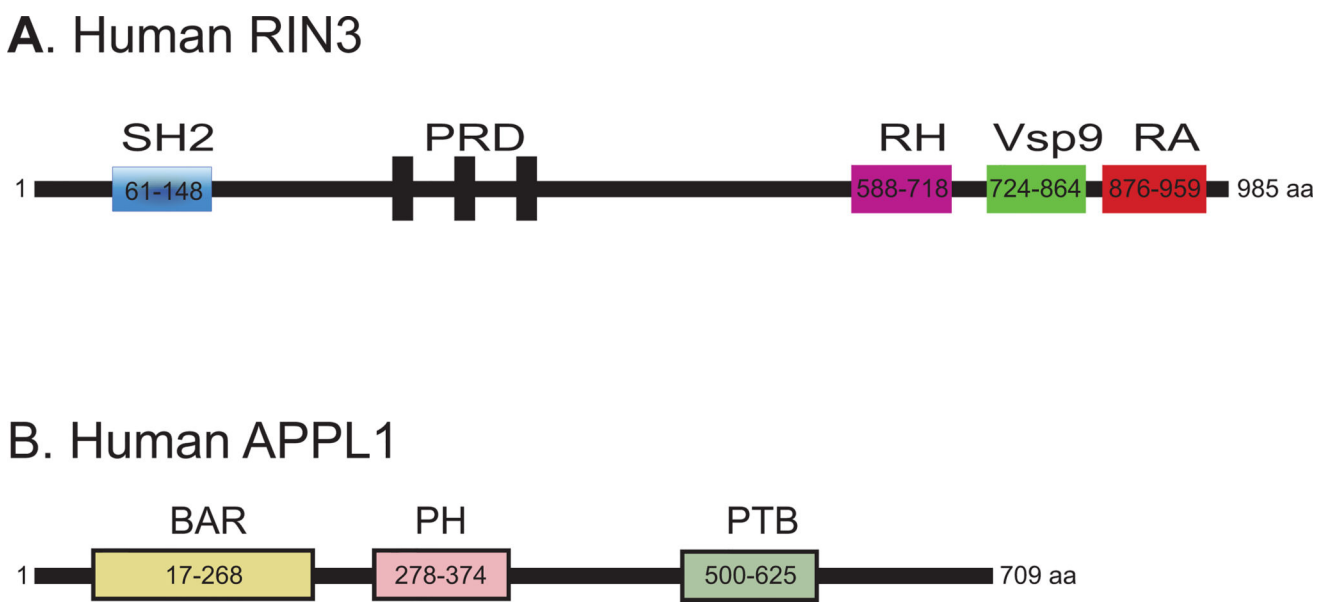

Figure 3.

Domain structures of RIN3 (A) and APPL1 (B). A: RIN3 is consisted of a SH2 domain (a Src homology 2 domain), a proline rich domain (PRD), a RIN-homology domain (RH), a Vsp9 domain [vacuolar protein sorting-associated protein 9 domain that is conserved in the catalytic domains of the Rab5 GEFs (Vps9p, Rabex-5 etc.)], and a Ras-association domain (RA)[88,89]. B: APPLI contains a BAR (Bin/Amphiphysin/Rvs) domain, a PH (pleckstrin homology) domain and a PTB (phosphotyrosine-binding) domain[148].