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Review

Exploring the potential role of rab5 protein in endo-lysosomal impairment in Alzheimer's disease

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ABSTRACT

Growing evidence suggests that neuronal dysfunction in the endo-lysosomal and autophagic processes contributes to the onset and progression of neurodegenerative diseases such as Alzheimer's disease (AD). Since they are the primary cellular systems involved in the production and clearance of aggregated amyloid plaques, endo-lysosomal or autophagic equilibrium must be maintained throughout life. As a result, variations in the autophagic and endo-lysosomal torrent, as a measure of degenerative function in these sections or pathways, may have a direct impact on disease-related processes, such as Aß clearance from the brain and interneuronal deposition of Aß and tau aggregates, thus disrupting synaptic plasticity. The discovery of several chromosomal factors for Alzheimer's disease that are clinically linked to regulation of the endocytic pathway, including protein aggregation and removal, supports the theory that the endo-lysosomal/autophagic torrent is more susceptible to impairment, especially as people age, thus catalysing the onset of disease. Although the role of endo-lysosomal/autophagic dysfunction in neurodegeneration has progressed in recent years, the field remains underdeveloped. Because of its possible therapeutic implications in Alzheimer's disease, further study is needed to explain the possibilities for effective autophagy regulation.

1. Introduction

Alzheimer's disease (AD), the most prominent cause of dementia in elderly individuals, is among the highest prevailing neurodegenerative diseases. It occurs predominantly in the regions responsible for complex cognitive activities and eventually demolishes the memory of patients and their standard of living. Pathologically, the neuronal regions of AD cases were predominantly differentiated due to matter of two characteristic proteinaceous masses that is, cytosolic neurofibrillary tangles (NFTs) and trans membranal amyloid-beta (Aß). Upon the advancement of the disease, impaired zones of the brain catalyze noxious actions that are characterized due to significant cognitive decline and memory deficits [1]. The polygenic variations in amyloid precursor protein (APP) and presenilins (PSEN-1 and PSEN-2) cause early-onset familial AD (EOFAD). Mutations in these three genes have a high penetrance (>85%) and are typically autosomal dominantly transmitted. Although, mutations in these genes can only account for a small percentage of EOAD cases (5–10%) [7,12], more than half of Mendelian cases [7, 13–15]. Despite the fact that ageing is a primary root cause of Alzheimer's disease, the overwhelming proportion of AD patients exhibit sporadic development without a direct relationship to familial origin. Although Aß can be formed on the cell lamina, the majority of Aß is created in the cytoplasm by endosomal activities. Aß deposits become insoluble Aß aggregates on the membrane as the disease progresses [2]. Neurofibrillary tangles, on the other hand, are mostly caused by tau protein hyperphosphorylation. Neurons with aberrant endocytic

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pathways show up before Aß aggregation, indicating that it plays a role in disease pathophysiology [3]. Endocytosis operates in conjunction with the lysosomal and autophagic pathways to degrade or reprocess proteins. The autophagic route, in which cytosolic components are destroyed by lysosomal processing to eliminate matured cells and proteins, is the most well-maintained metabolic system [4]. The human autophagic system is present in normal settings, but it becomes overexpressed in pathological stages in response to certain stressors, such as Aß accumulation in an attempt to reduce spare protein burden [5]. Pre-clinical models have also manifested that impairment in autophagic/endocytic pathway along with the uncontrolled trafficking of matured cells and proteins are observed to catalyze AD [6,7]. Dysfunctions associated with autophagic/endocytic pathway involving dysregulated pH of lysosomes, APP-linked and non-linked lysosomal deformities, storage-linked problems, impairment in cathepsin-D functioning, cholesterol aggregation, neurotrophin impairments, as well as an impaired endothelin-converting enzyme, all observed to involve significantly in initiation or advancement of neurodegeneration as implicated in AD. Therefore, it becomes essential to investigate the above-mentioned processes for remoter comprehension of the pathological basis of AD. The review discusses the physiological and pathological basis, along with the significance of therapeutic approaches associated with the autophagic/endo-lysosomal system [8].

2. Physiological roles of endosomal-lysosomal system

In general, the endosomal-lysosomal network is a part of the endocytic pathway, which includes several components that govern protein degradation. Autophagy and phagocytosis are intricately linked to this network. The lysosome is where these mechanisms come together for ultimate protein breakdown [9,10]. The endocytic pathway involves early/late endosomes, lysosomes that operate simultaneously to control protein reprocessing and recycling lysosomes. Endosomes are the chief elements of endosomal processing that can face structural & physiological alterations to meet the requirement for initiating the process of protein regulation by removing unnecessary proteins [11]. The production of vesicles, in which clathrin-coated pits sprout from the cell membrane and eventually form clathrin-coated vesicles, initiates endocytosis. Early endosome antigen 1 (EEA-1), Rab5, rabaptin-5, and protein families of bovine antimicrobial protein-1 (BAMP) affect the ability of such vesicles to merge with early endosomes [12]. Early endosomes are a critical sorting stage that governs how protein cargos are transported into various organelles. The delivery of proteins to late endosomes is known to be mediated by early endosomes for lysosomal degeneration. The primary role of the early endosome is to guide protein cargos to late endosomes and subsequently to lysosomes for destruction. The sprouting of intrinsic vesicles to inwards and the creation of intraluminal vesicles start the development of early endosomes to late endosomes. The development of multivesicular bodies (MVB) follows the synthesis of intraluminal vesicles. Such pathway is observed to be activated from ubiquitin which is further regulated by the endosomal sorting complex required for transport (ESCRT-1) [13]. As the endosome matures, the replacement of interaction between vesicles and Rab5 by vesicles and Rab7 will occur, which is commonly referredto as “Rab conversion” [14]. As thedevelopment of endosomes is finished,the fusion of late endosomeswith the lysosomes takes place that is regarded to be the last phase for protein degradation. Lysosomes can receive digestive enzymes and hydrolases straight away from Trans Golgi Network (TGN), which is controlled by a system called a “retromer”. As these systems necessitate an environment with low pH to perform, the

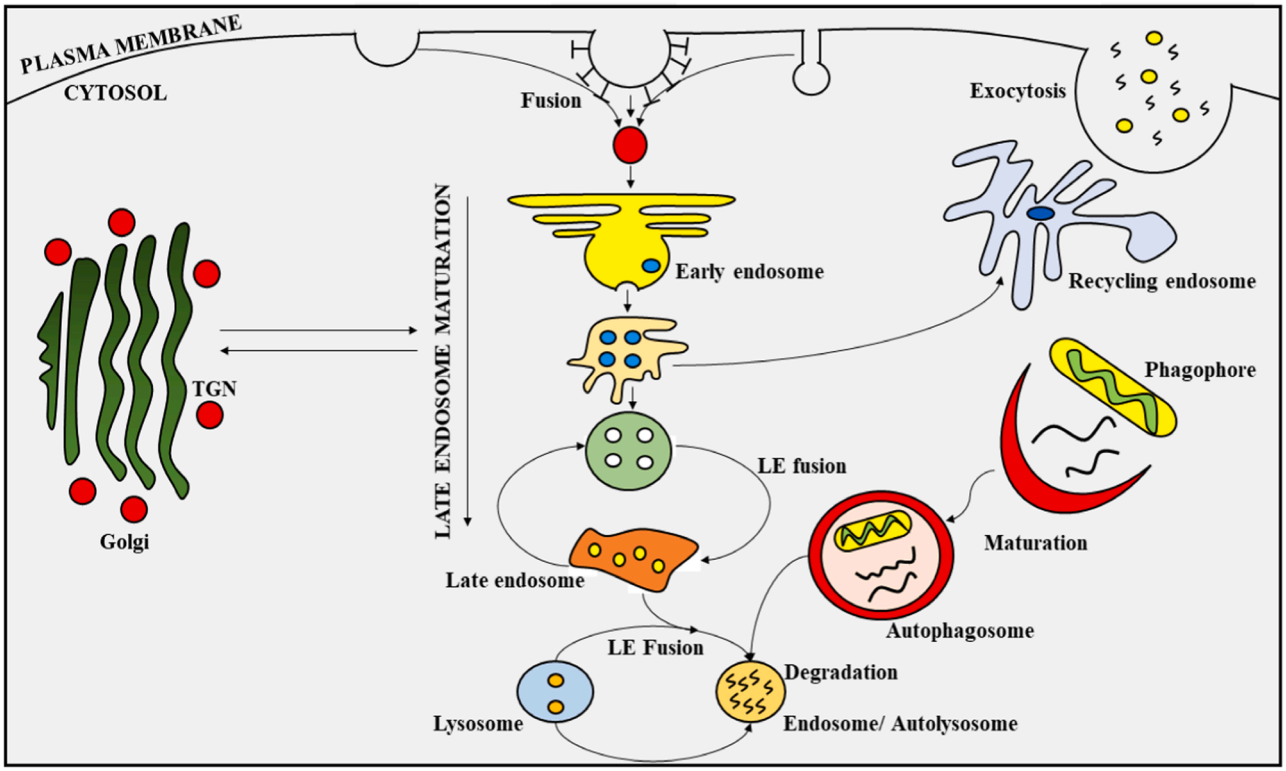

Fig. 1. The endo-lysosomal system. The primary endocytic vesicles deliver the proteins to early endosomes in the peripheral cytosol. After a lag period during which the early endosomes deposit load and start recycling to the cell membrane, the transformation of the early endosomes to late endosomes occurs. The nascent late endosomes carry a specified set of endocytosed loads from the early endosome, which is combined with recently produced surface components and lysosomal hydrolases from the secretory pathway through homotypic fusion reactions. Their role is to supply the secretory and endocytic components to lysosomes. The fusion of an endosome and a lysosome produces a transitory hybrid vesicle, the endo-lysosome, which performs active degeneration. The endolysosome is matured to a classical dense lysosome, which possesses a storage vesicle for surface components and lysosomal hydrolases. LE- Late endosomes; EE- Early endosomes.

endosomal and lysosomal surfaces provide an ideal acidic habitat for protein degradation [11] (Fig. 1). The activation of ATP-dependent proton pumps in both the membranes of endosomes and lysosomes help to maintains the pH in the range of 6.5–4.5. [15]. Recycling endosomes in this process controls the transport of trans membranal fats from the Rab5 endosomes in order to reutilize lipids for the cell. Recycling endosomes return the lipids towardsthe bilayer surface which processes under the regulation of Rab11 [16,17]. Besides, protein loads can be transported in a retrograde manner which involves the transfer of protein loads from the Rab5 endosomes towards TGN that is controlled by retromer. The importance of this system in the regulation of protein degeneration portrays that any irregularities/dysfunction in these processes results in major problems in the brain as a result of abnormal deposition of unusual proteins in the neurons which eventually causes neuronal toxicity [18].

3. Endo-lysosomal dysfunction in AD

Genetic mutations that regulate the function of the endosomal-lysosomal pathway result in a multitude of disorders inclusively called lysosomal-storage disorders (LSDs). Surprisingly, LSDs exhibits strong phenotypic overlapping with AD, especially in the deposition of lysosomal vesicles, uprooted dendrites, dystrophic axons, cognitive failure, and neurodegeneration [19]. Both familial and sporadic AD is identified through the continuous growth of amyloid-ß (Aß) aggregates and neurofibrillary tangles (NFTs) of hyperphosphorylated tau protein in and out of the neurons. These indicators arise comparatively late in the disease, thus proposing the discussion that whether they result from an existing pathogenic mechanism. The intracellular deposition of Aß proteins, the chief components of amyloid/senile plaques, actually paves the way for plaque generation. Accumulation-prone Aß42 also aggregates in multivesicular bodies (MVBs) in neurons during the initial stages of the disease [20]; which is noticed together with dysfunctional endocytic pathways such as the enhanced measure of Rab GTPase that assist an increase in activity of endocytic pathway [21], altered generation of Rab11-possessing vesicles [22], and impaired activity of lysosomes [23,24]. The deformities in the endocytic pathway largely correspond with AD-linked early synaptic and memory loss as do amyloid aggregates [25]. The generation of Aß from the amyloid precursor protein (APP) in the related regions reveals a clear relationship between Aß and the cellular endolysosomal trafficking pathway. The APP is processed by the action of ß- and Γ- secretases, a tetrameric system that includes nicastrin (NCT), anterior pharynx-defective 1 (APH-1A/1B), presenilin-1/2 (PSEN-1/2), and presenilin enhancer 2 (PSEN2) [26]. Within cells and tissues, these four main Γ-secretase complex forms coexist. [27]. The prominent environemnt for these enzymes facilitates a significant influence on APP metabolism. The ß-secretase enzyme is designed to work best at low pH since the amyloidogenic pathway is thought to take place mostly in endocytic areas, where the produced Aß is reprocessed and released [28,29]. On the other hand,α -secretase, which is found in TGN and extracellular environment [30], is involved in the processing of APP and suppresses the production of Aß peptide. Different sections of APP are transported to endocytic processing, where they are degraded sequentially to produce particular Aß segments, resulting in a cytosolic pool of pathogenic Aß [31]. The significance of these cytosolic deposits as a stimulus for extracellular accumulation is supported by the fact that the cytosolic Aß deposits reappear following immunotherapy-mediated exhaustion of cytosolic and laminal plaques [32]. Notably, the cytosolic Aß deposits are largely generated by PSEN2/Γ-secretases as they occur in late regions of endosomes [33]. Such special physiology is regulated via distinctive amino-terminal division patterns in PSEN2, but not in PSEN1, which is involved in the categorization of the AP-1 adaptor complex between the TGN and late regions of endosomes. Ironically, a range of mutations in PSEN1 switches the position of Γ-secretase to the late endosomal system from the plasma membrane and endosomes, thus enhancing the cytosolic Aß deposits and suggesting various pathways for FAD-linked mutations in PSEN1. Generally, FAD-linked mutations in APP and the PSEN genes generate more of the protracted Aß peptides, emphasizing that it does not increase the entire Aß mass rather in the outline of Aß which is greatly related to the initiation and advancement of disease [34]. Till now, genome-wide association (GWA) researches recognized twenty seven AD-linked genes, including, ADAM10, CR1,MAPT, APOE,BIN1, NME8, PICALM, PLD3, TREM2, SORL1, ABCA7, DSG2,IQCK,ACE2, ADAMTS1 [35,36]. With novel identification strategies and procedures being advanced, ancillary high confidence applicant genes are being developed such as CLCN-, CHRD, CPAMD-8, GRN, GRID-2IP, HLA-DRA, HDLBP, MAS1L, NLRP-9, MS4A-3, WDR-76, RABEP-1, and SCIMP [37–39]. When sorting these LOAD risk factors based on cellular processes it is evident that several pathways are associated directly with subcellular transporting pathways, specifically to the endocytic system. In particular, the association of APOE4, INPP-5D, ABCA7 with the transport of cholesterol, whereas CLU and TREM2 are physiologically related to the removal of foreign particles through immune cells. Contrastingly, BIN1, RIN-3, CD2AP, SORL-1, and PICALM all seem to have a role in the regulation of endocytic transport, while PLD-3 and GRN are transported towards lysosomes [40,41] (Fig. 2). As a result, a debate may arise about lysosome imbalance, which is a common signal in both early and late-onset AD. For example, in acidic areas (as in familial-AD), the formation and accumulation of cytosolic hazardous Aß-42 variant might progress Aß accumulation to higher molecular weight species, which can generate amyloid oligomers and perhaps disrupt cellular membranes [42,43]. Late-onset AD-linked risk factors, on the other hand, may impair the function and stability of endolysosomal transport, influencing secretase and APP transport and slowing the clearance of APP segments and tangles through a decrease in endosomal-mediated degeneration. Some of the genetic factors associated with the onset and progression of the disease are described in Table 1.

4. Rab dysfunction in AD

Rabs are smaller proteins that belong to the superfamily Ras and are observed within various compartments of the cytosolic vesicular system. Up to 60 mammalian Rabs were discovered, being a substantial and more diversified family of the Ras superfamily [81,82]. Rab proteins occur in every eukaryotic cell, varying from the most developmental preserved which are extensively involved in vesicular transport to the most differentiated ones that are only located in some human cells [83,84]. Rab proteins interchange between an active surface-bound phase (GTP-linked) and an inactive cytoplasmic phase (GDP-linked). To shift between these phases, Rabs need effector proteins known as GEFs (Guanine nucleotide exchange factors). When in the GTP phase, Rab mobilizes activator proteins which allow the regulation of various functions of vesicular transport such as load selection, restraining, transporting, and docking. Once the process is finished, Rab-GTP is metabolized via GAPs (GTPase activating proteins) to recycle to the GDP phase. Here, Rab-GDP is returned to the surface via tethering to Rab GDIs (GDP disassociation inhibitors), which decide the exact location & expression of Rab proteins [85,86]. The large quantity of elements of the Rab family shows the heterogeneous nature of the cytosolic vesicular transport pathways, consequently assigning the Rab proteins to only or varied regions. In particular, Rab5 portrays a significant function in the endocytic pathway via transferring loads to different organelles [87], while Rab23 negatively regulates the Sonic hedgehog-signaling pathway [88].

Rab5 proteins are essentially involved in cellular homeostasis by interacting with several effector proteins namely, phosphotyrosine binding domain (PTB), leucine zipper motif [89] early endosome antigen 1 (EEA1), Rabaptin-5/Rabex-5, and phosphatidylinositol 3-kinases (PI3K), [90]. These effectors characteristically attach to the active state of Rab and control binding of the early endosomes [91]. Hence, Rab5 plays an essential function in endosomal transport [92].

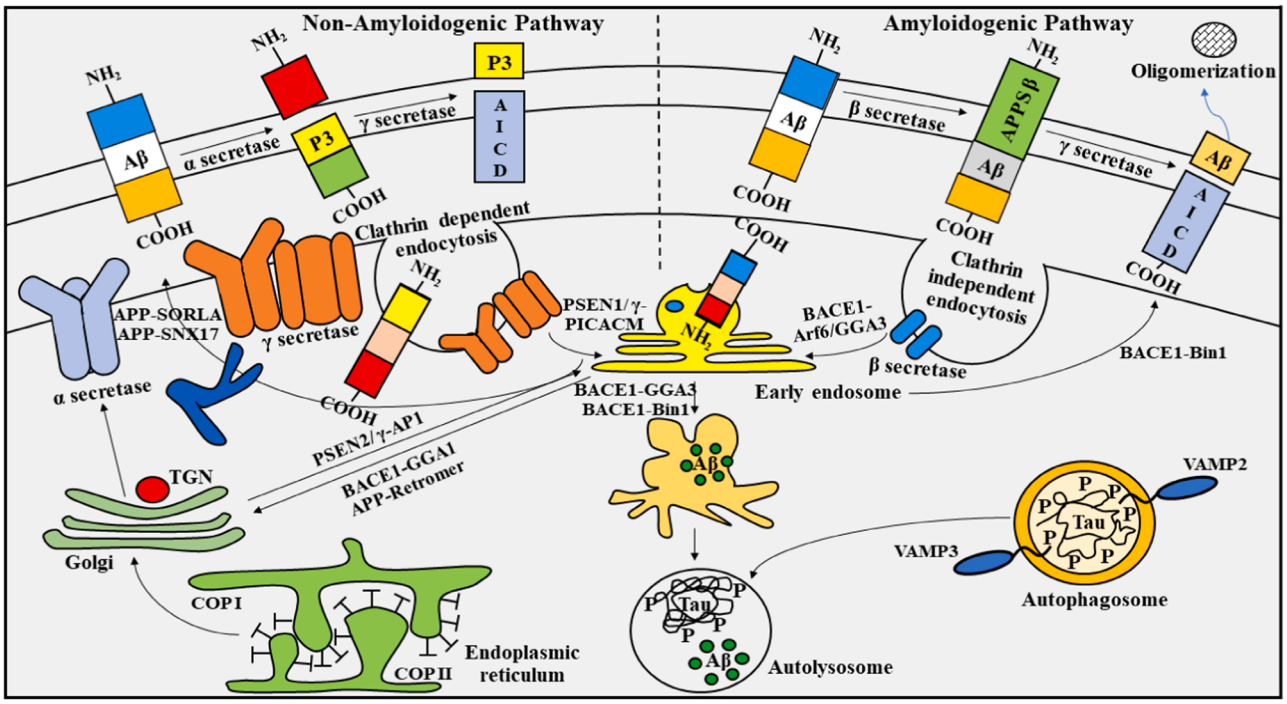

Fig. 2. The structural synchronization of an amyloidogenic and no-amyloidogenic pathway for APP. non-amyloidogenic pathway initiates with APP shedding largely at the cell membrane but as well in the trans-Golgi network (TGN). Hereunder, the remaining carboxyterminal fragments are metabolized by Γ-secretase to generate benign p3 peptides and an intracellular domain. In the amyloidogenic processing, which is more predominant, APP is processed first by BACE1 mostly in endosomes which are spatially controlled by BACE1. The ultimate processing results in the generation of various Aß proteins of which the Aß42–43 are more accumulation-prone. Both the processes are controlled by various genes such as PSEN1–2, PICALM, BIN1, CD2AP. APP- amyloid precursor protein; Aß- amyloid-beta; TGN- trans-Golgi network; AICD- amyloid precursor protein intracellular domain; CTF- carboxy-terminal fragments; p3- amyloid peptide; VAMP3- vesicle-associated membrane protein; PSEN- presenilins; BACE- beta-site APP cleaving enzyme; COP- coatomer protein; PICALM- Phosphatidylinositol binding clathrin assembly protein; BIN- bridging integrator; GGA1- Golgi associated, gamma adaptin ear containing, ARF binding protein 1.

Continuous activation of Rab5 causes its interaction with the class C VPS/HOPS (Vacuolar protein sorting/homotypic fusion and protein sorting) complex, a well-formed GEF for Rab7. that resides over the surface of late endosomes, thus resulting in the transformation from $Rab5^{+}$ early endosomes to $Rab7^{+}$ late endosomes for degeneration. Consequently, the period for which Rab5 remains in its active state is firmly controlled so that a continuous transformation between endosomes which is principally vital for neuronal neurotrophic signals. Substantial research has revealed that neurotrophins like nerve growth factor (NGF) tether to tyrosine kinases(Trk) receptors to get incorporated in $Rab5^{+}$ endosomes which transport essential signaling proteins like extracellular-signal-regulated kinases (Erk), phospholipase-C (PLC), and phosphoinositide 3-kinase (PI3K) to transmit the neurotrophins to the nucleus and cytoplasm [93]. Several experimental investigations have shed light on an intriguing debate over the conversion of signaling endosomes to Rab5 + endosomes without proceeding to Rab7 + endosomes during their transport in neurons. This is explained by NGF stimulation, in which a GTP-Rab5 is converted to GDP-Rab5 after Trk-A mediated engagement of Rab-GAP to keep GTP-Rab5 in control, preventing Rab5 to Rab7 conversion [94]. As a result, NGF/TrkA signaling endosomes are protected against premature degeneration. With Rab5 performing multiple critical activities in regressive endosomal categorization and transportation, it is possible that the expression of Rab5 is disrupted in the early stages of AD, as suggested by recent research. [95,96] as well as in animal models of other neurodegenerative diseases such as Parkinson's disease (PD) [97]. Continuous overactivation of Rab5 disturbs various endosomal processes including endosomes, autophagy, and lysosomes processing that all have been located disturbed in AD [98](Table 2). A chief outcome of these alterations in the pathological states leads to early degeneration of the signaling of neurotrophins, hence strongly prohibiting the conveyance of regressive neurotrophic signals to the neurons, resulting in cerebral atrophy, which is certainly the case of premature degradation of basal forebrain cholinergic neurons in AD [99]. Abnormal retromer is also observed in AD [100]. Retromer is a proteinaceous complex that regulates endosome to-Golgi transport. The measure of vacuolar protein sorting (Vps26 and Vps35), the essential retromer, was substantially decreased in the cortical region of the brain of AD patients [101]. The sorting receptor (SorLA) is a cerebral protein that also regulates APP transport from endosomes towards Golgi. Hence, the defective retromer together with a decreased measure of SorLA could aggravate in impairment of APP trafficking from endosomes to Golgi, leading to endosomal aggregation of APP. Inside the endosomal regions containing hydrolytic enzymes, APP is metabolized with ß-secretase to produce β-CTF and Aß peptides. The reprocessing endocytic system directed by Rab4/Rab11 which mediates cytosolic classifying, transporting, and metabolism of APP has also been observed a change in AD [102]. The disturbance of principal neuronal-specified cytoplasm-to-axon endocytic pathway was proposed to be the result of deposition of ß-CTF components [103]. Utilizing induced totipotent stem cells from human neurons with known AD mutations in APP and PSEN1, the latest research has shown that subcellular sorting and transporting of APP was impaired in these neuronal cells. Moreover, reducing the levels of Rab11 produced a reminiscent impairment in neuronal transport of APP in experimental neurons [104]. Such research indicated that Rab11 plays a crucial function in neuronal trafficking, thus its impairment possibly result in the initial stages of AD.

A distinct earliest pathogenesis of AD involves impairment in endosomal functioning and was reported in AD patients preceding the accumulation of extracellular amyloid (Aß) plaques [105]. Such uncoverings propose that neurons get damaged intracellularly before any plaque generation or neurofibrillary tangle formation in the brain.

Table 1
The various genetic risk factors implicated with the onset and progression of AD.

S. No	Risk factor	Forms/ Types	Physiological roles	Implications in AD	References
1.	APOE (Apolipoprotein)	APOE 2 APOE3 APOE4	• APP metabolism • Uptake of extracellular Aβ to enhance Aβ clearance	• Aß deposition into insoluble plaques • Epigenetic alterations • Disturbed endosomal pH because of negative expression of Na^+ / H^+ exchanger NHE6. • Decreased LRP8-Reelin interaction thus causing synaptic dysfunction • Upregulated $Rab5^+$ early lysosomes and endosomes	[44–49]
2.	TREM2 (Triggering Receptor Expressed on Myeloid Cells-2)	TREM 1 TREM 2	• Regulation of auto-immunity • Suppression of macrophage production • Anti-inflammatory response	• Impaired clearance of Aβ plaques • Impaired endo-lysosomal functioning as such in APOE dysfunction • Dysregulation of TREM2 can result in impaired mTOR signaling. Thus, leading to the production of autophagic vesicles as noticed in the brains of AD patients.	[50–53]
3.	PSEN (Presenilin)	PSEN 1 PSEN2	Regulates the catalytic function of Γ-secretase complex	• Enhanced generation of Aβ42 peptides thus leading to aggregation of Aβ in form of amyloid plaques • Impaired interaction with sorting signals, hence affecting categorization of multivesicular bodies and late-endosomes.	[54–59]
4.	Neurotrophins	Rab (Rab5 and Rab7)	• Retrograde trafficking of nerve growth factor (NGF)- mediated Tropomyosin receptor kinase-A (Trk-A) receptor • Regulates sustenance of basal forebrain cholinergic neurons (BFCN)	• Degeneration of BFCN (BFCN loss) with cognitive decline • Hyperactivated Rab5 will cause enlargement of early endosomes • Impaired biogenesis of signaling endosomes, thus causing BFCN atrophy • Impaired synaptic plasticity • Memory and learning plasticity • Apoptosis	[58,59]
5.	Retromers	Vps 35 Vps 29 Vps 26 Vps 5 Vps 17	• Recognition of cargo proteins with the help of cargo-selective complex • Involved in the retrograde pathway	• Impaired retrograde pathway thus leading to BFCN atrophy • Impaired endo-lysosomal pathway • Persistent activation of endocytic and autophagic systems as observed in AD.	[60,61]
6.	ESCRT (Endosomal sorting complexes required for transport)	ESCRT-0 ESCRT-I ESCRT-II ESCRT-III	• Initiating the degeneration of proteins via identification and classification of endosomal proteins bind with ubiquitin for degradation • Synthesis of MVB (multivesicular bodies)	• Impaired endo-lysosomal pathway as seen in AD • Delayed maturation of early endosomes to lysosomes, leading to protein accumulation (such as Aβ protein)	[62,63]
7.	ECE (Endothelin converting enzyme)	ECE-1 ECE-2	• ECE1 regulates both intracellular and extracellular Aβ levels • Regulates the hydrolyzation of endogenous Aβ	• Accumulation of cytosolic Aß in the vesicles of the endocytic system. • Synaptic dysfunction and neuronal loss	[64,65]
8.	PICALM (phosphatidylinositol binding clathrin assembly protein)		• Involved in regulation of membrane processing via the adaptor complex 2 (AP2) to clathrin-coated pits. • Regulates the structural activity of VAMP and their location in endosomal regions • APP processing	• Decreased PICALM levels lead to autophagic dysfunction • PICALM co-localizes with Tau tangle burden as observed in AD • Impaired APP processing may lead to abnormal Aβ production and aggregation as plaques	[66–73]
9.	BIN1 (Bridging integrator 1)		Implicated with endo-lysosomal transport in neurons and in enzymatic processing of APP to regulate Aβ generation	• BIN1 dysfunction can cause a build-up of neurofibrillary tangles (hyperphosphorylated tau) • Reduction in lysosomal activity. • Revoking the induction of autophagy or causing physical damage to the vesicles.	[74–77]
10.	PLD3 (Phospholipase D-3)	PLD 1 PLD 3 PLD 4	• Linked with endosomes to Golgi retrieval • Processing of APP • Maintenance of endolysosomal functioning	• Impaired APP processing leading to the production of Aβ and accumulation of amyloid plaques • Impaired lysosomal homeostasis • Increased densities and dimensions of primary and secondary lysosomes	[78–80]

Endosomal dysfunction observed in AD brains involves enlarged early endosomes which contain Rab5 protein and thus enhance endocytosis [106]. Experimental data has also strengthened the basis of the association between neuronal APP and Rab5-possessing early endocytic dysfunction [107]. APP, which is a major protein indicated in AD, is a luminal protein which is processed initially with α- or ß-secretase to form the analogous COOH-terminal components(ß-CTF/α-CTF) and then with Γ-secretase to produce the APP intracellular domain (AICD) & subsequently Aß proteins. The various APP genes and cleaved components like APP and COOH-terminal components were observed directly linked with the early endosomal abnormalities of AD [108]. Recently, evidence has emerged that excessive APP and ß-CTF, but not AICD or -CTF, increases Rab5 expression, resulting in a larger early endosome in primary basal forebrain cholinergic neurons (BFCNs), which degrades initially in Alzheimer's disease. [109,110]. Significantly, these outcomes have indicated a function performed by APP ß-CTFs in causing neuronal toxicity through the deposition of toxic APP products.

Nerve growth factor (NGF) is a target-based neurotrophin that functions through trans membranal tropomyosin kinase A (TrkA) receptor for proper distribution and integrity of BFCNs[111] by controlling the activity of cytosolic and genetic pathways essential for the phenotype of BFCN, such as cell diameter [112]. After endocytosis, the NGF/TrkA signaling systems are transported to $Rab5^+$ endosomes and then to the soma in a regressive manner to produce NGF signals. Hence,

Table 2
Pre-clinical evidences for rab5 dysfunction in Alzheimer's disease.

Model	Stimulus	Rab 5 overactivation consequence	Result	Reference
Embryonic mouse cortical neuron from E17-E18 pregnant C57BL/61 females	Rab5 effector APPL1 (adaptor protein containing pleckstrin homology domain phosphotyrosine binding domain and leucine zipper motif) mediates Rab5 overactivation; caused by increased levels of β-cleaved carboxy-terminal fragment of APP (β-CTF)	• Endosomal enlargement • Impaired axonal transport of endosomes • Failure of retrograde neurotrophin signaling	Knockdown of APPL1 corrects these endosomal impairments caused by overactivated Rab5	[115]
Rab 5 overexpressing transgenic mouse	APP- βCTF trigger in a Thy-1 promotor	• Accelerated endocytosis • Increased endosome fusion • Reduction in levels of surfaces AMPARs and acceleration of their endocytosis • Tau hyperphosphorylation due to downregulation of pro-survival AKT pathway, thus leading to increased GPK-3β activation • BFCN atrophy and memory loss	Rab5 overactivation induces endosomal dysfunction and hence reducing elevated levels of APP- βCTF to normalize RAB5 overactivation has shown to reduce endosome and cholinergic deficits	[116]
Brain samples from a total of 38 postmortem human subjects	AD patients with enhanced Rab5 expression	• Prodromal increase of the early endosome • Reduced BFCN levels	Endocytic pathway abnormality in initiation and progression of AD reflecting upregulation of Rab GTPases in basal forebrain and hippocampus	[117]
APP/PS1 transgenic animals	Rab5 overactivation by increasing levels of RIN3	• BFCN degeneration • Increased diameter of Rab5 endosomes • R1N3 recruits CD2AP and BIN1 to early endosomes • Tau hyperphosphorylation • Impaired trafficking and processing of APP	In the absence of RIN3 overexpression, signals for CD2AP and BIN1 were mostly diffused across the cytoplasm with little or no Rab5-early endosomal enlargement	[118]
PC12 Cells and cultured rat BFLNs	Excessive APP- βCTF expression	• Endosomal enlargement • Disrupted NGF signaling and axonal trafficking in BFCN	Dysregulation of Rab5 activity contributes significantly to the early pathogenesis of AD	[119]

neuronal trafficking regulated by $Rab5^{+}$ endosomes performs an important function in supporting the trophic state of BFCNs. Some variations in this signaling possibly disturb axonal trafficking, leading to neurodegenerative disorders such as AD. Such indications have further evidenced the role of overexpressed Rab5 to axonal trafficking impairment and neuronal atrophy in AD [113]. Although, during pathological states, BFCNs are stuffed with imprudent APP and its components, that successively cause inclined GTP-Rab5 levels, thus resulting in prolonged Rab5 hyperactivation. Overexpression of Rab5 causes an increase in the size of early endosomes which disrupts endosomal transport of APP, thus aggravating its cleavage. Moreover, an impaired increase in the size of $Rab5^{+}$ endosomes may disturb the regressive neuronal transport of NGF signals. The total impact of all such functions of APP fragments will be decreased trophic signals being transported to the cytoplasm, hence resulting in neurodegeneration as observed in AD [114](Fig. 3).

5. Therapeutic implications

The study of prodromal phases of AD postulates that AD initiates quietly 10 years before apparent dementia and observable neuropathological implications [120,121]. Despite the expanding acknowledgment that interference at the preliminary stage is possibly required ineffective treatment of AD, the biological studies of the preliminary phases of AD have not been understood properly. Contrastingly, Rab5-linked endosomal impairment takes place prematurely in AD [122] and has been believed to involve in the preliminary stage, though its impact on the neurodegenerative stage of the disease was not examined [123]. Also, a soluble configuration of Aß peptide at the preliminary phase is generally suggested activating the neurodegenerative stage of AD by assisting the dysfunction in tau equilibrium [124]. Nonetheless, studies proposing Aß as the chief preliminary factor involved in the advancement of the disease have been reduced, despite mastering the consideration for therapeutic implications in AD. Various researches consider Rab5 overexpression for its therapeutic potential in AD and additionally indicate that elements of the several cell signaling pathways mediating Rab5 activation or deactivation [125], as a supplementary class of possible therapeutic agents.As the acidity of lysosomes is essential for the activity of its enzymes for protein degeneration and their fusion with lysosomes, it is urgent to recognize possible therapeutic targets that may regulate lysosomal acidity. For example, it can be attained by increasing the activity of cyclic adenosine monophosphate (cAMP) via stimulation of adenylyl cyclases (cAMP producing enzymes) and hindrance of phosphodiesterases (cAMP degenerating enzymes) [126]. By increasing the cAMP levels by this mechanism, protein kinase A (PKA) gets stimulated which results in an incline of levels of unbound Zn^{2+} in lysosomes. The increased concentration of unbound Zn^{2+} will adjust the lysosomal pH [127]. A single agent that is clinically utilized at present is colforsin, a hydrophilic derivative of forskolin that is used as a therapeutic agent in asthma. As for the hindrance of PDE, cilostazol, a PDE3 inhibitor is observed to adjust the pH of lysosomes together with advancement in autophagic torrent in glial cells. Cilostazol also enhances the amounts of unbound Zn^{2+} in lysosomes and promotes its chelation with a PKA inhibitor that reduces the effects of cAMP. Therefore, there is a potential for the occurrence of a monotonous association among cAMP, Zn^{2+}, and acidity of lysosomes.A retromer portrays an essential function in mediating the activity of astrocytes and synaptic plasticity, it is significant to sustain its stability and activity. Any impairment in the elements of the trimeric core of the retromer system will result in considerable suppression of other components as well [128]. Chaperones are utilized as a therapeutic agent to support the retromeric system as they can directly bind with retromers and inhibit its degeneration. The 2 thiophene thiourea forms selectively bind to and balance the retromer system in opposition to thermal degradation, which also enhances the retromeric concentration in the hippocampus [129]. The elevation of the activity of retromer will assist trafficking of APP from the endosomes and inhibit the aggregation of Aß peptides in the neurons. Studies manifesting the increase in function of retromer are demonstrated that it cannot induce toxicity in experimental models [130,131]. As the autophagy pathway is essential in regulating protein degeneration or clearance in the neurons, it can be utilized for the treatment of several neurodegenerative diseases like AD in which neuronal deposition of proteins portrays a crucial role in the

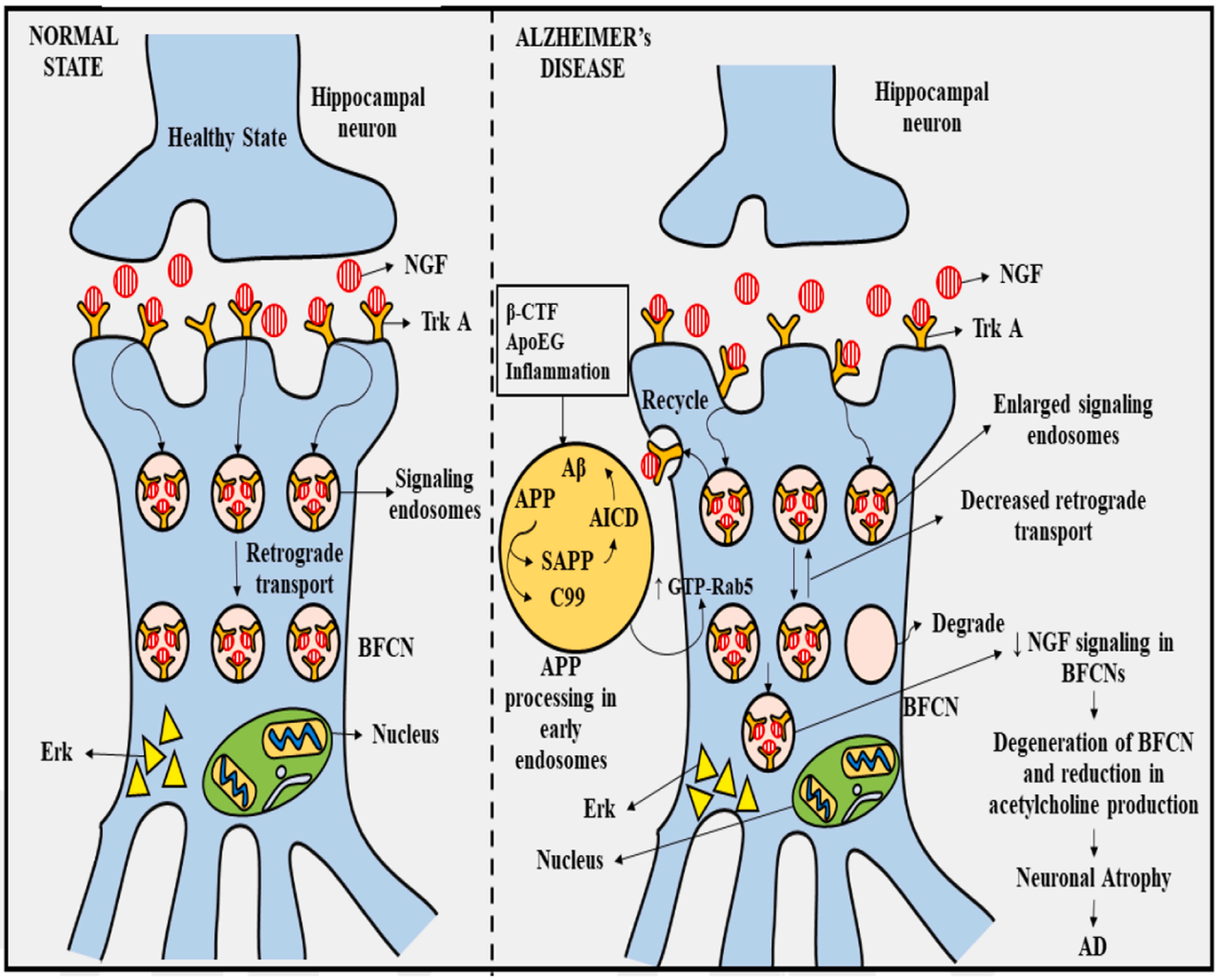

Fig. 3. The suggested models of retrograde neuronal transport role in NGF signaling endosomes under normal physiological states and stages of AD. In the case of AD, basal forebrain cholinergic neurons (BFCNs) are observed with abnormal APP and APP ß-CTF amounts, which in turn leads to elevated levels of GTP-Rab5, thus resulting in prolonged Rab5 overactivation. Overexpression of Rab5 catalyzes an increase in the size of early endosomes that hamper the endocytic transport of APP, further aggravating its processing. Also, enlarged early endosomes possibly interfere with retrograde neuronal transport of NGF signals. The overall result of all these effects of APP and APP ß-CTF will be decreased trophic signals being conveyed to the cytoplasm, which ultimately induces neuronal atrophy as implicated in AD. APOE- apolipoprotein E; BFCN- basal forebrain cholinergic neurons; NGF- nerve growth factor; APP- amyloid precursor protein; Rab- Ras-associate binding protein; Erk- extracellular-signal-regulated kinase; Trk A – tropomyosin receptor kinase A; Aß- amyloid-beta; CTF- carboxy-terminal fragment; sAPP- soluble amyloid procure protein; AICD- amyloid precursor protein intracellular domain.

neurodegenerative cascade. Physiological stages of autophagy in neurons are crucial for the degradation of Aß plaques and NFTs [132]. To date, there has been an enormous endeavor to use autophagy activation in preclinical models of AD using autophagy-inducing drugs. For example, rapamycin is a major inducer of autophagy which may prevent activation of the mTOR kinase pathway in a mouse model, which leads to a considerable decline in the measure of NFTs and Aß plaques [133]. Another autophagic-inducer is Trehalose, which stimulates mTOR-dependent/independent autophagic pathway. It significantly decreases the degree and toxicity of intraneural deposited tau [134]. Administration of nanoparticle, Graphene oxide (GO), improves cognition in AD models by activating autophagy by inducing the PI3K/Akt/mTOR pathway, a pathway which is related to tau deposition [135]. Several categories of autophagy-inducing drugs have also been suggested which include nutraceuticals [136], antibiotics [137], lithium [138], miRNAs [139], and plant extract. In brief, autophagy-inducing agents are observed with positive outcomes in both experimental studies of AD and thus should be carried forward as a potential therapy in AD treatment. Furthermore, phosphorylation of serine by phosphokinase-C (PKC) was also observed to decrease the lysosomal trafficking of APP along with the generation of Aß-42 [140], which proposes that phosphorylation of serine changes the interplay between APP and AP-3. Besides the involvement in the serine phosphorylation, PKC is shown as a part of non-amyloidogenic processing of APP that inhibits the Aß generation which may catalyze AD [141,142]. Such outcomes manifested that the clinical adjustment of APP trafficking can be done to decrease the production of abnormal Aß peptides.

6. Conclusion

AD is a highly complex condition involving a variety of factors, cells, and pathways. These several factors may work alone or in combination to aid in the pathogenesis of Alzheimer's disease. It's become clear that the equilibrium of endosomal categorizing, transporting, and signaling, which is critical for maintaining neuronal integrity, is disrupted in Alzheimer's disease. The newly found risk factors for Alzheimer's disease that target the endo-lysosomal/autophagic pathways may highlight the role of endocytic pathway disruption in the early stages of AD

pathogenesis. Describing the interaction of genetic factors and pathways will not only increase our comprehension of the processes involved in early and late stages of neurodegeneration in AD and other related conditions but will also advance the discovery of novel targets for progressing therapeutic approaches for neurodegenerative diseases.

CRediT authorship contribution statement

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