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Koss, David J.; Campesan, Susanna; Giorgini, Flaviano; Outeiro, Tiago F.

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REVIEW

Dysfunction of RAB39B-Mediated Vesicular Trafficking in Lewy Body Diseases

David J. Koss, PhD,[1*] Susanna Campesan, PhD,[2] Flaviano Giorgini, PhD,[2] and Tiago F. Outeiro, PhD[1,3,4,5*]

[1]*Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK*
[2]*Department of Genetics and Genome Biology, University of Leicester, University Road, Leicester, UK*
[3]*Department of Experimental Neurodegeneration, Center for Biostructural Imaging of Neurodegeneration, University Medical Center Goettingen, Goettingen, Germany*
[4]*Max Planck Institute for Experimental Medicine, Goettingen, Germany*
[5]*Scientific employee with a honorary contract at Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Göttingen, Germany*

ABSTRACT: Intracellular vesicular trafficking is essential for neuronal development, function, and homeostasis and serves to process, direct, and sort proteins, lipids, and other cargo throughout the cell. This intricate system of membrane trafficking between different compartments is tightly orchestrated by Ras analog in brain (RAB) GTPases and their effectors. Of the 66 members of the RAB family in humans, many have been implicated in neurodegenerative diseases and impairment of their functions contributes to cellular stress, protein aggregation, and death. Critically, RAB39B loss-of-function mutations are known to be associated with X-linked intellectual disability and with rare early-onset Parkinson's disease. Moreover, recent studies have highlighted altered RAB39B expression in idiopathic cases of several Lewy body diseases (LBDs). This review contextualizes the role of RAB proteins in LBDs and highlights the consequences of RAB39B impairment in terms of endosomal trafficking, neurite outgrowth, synaptic maturation, autophagy, as well as alpha-synuclein homeostasis. Additionally, the potential for therapeutic intervention is examined via a discussion of the recent progress towards the development of specific RAB modulators. © 2021 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: RAB39B; Lewy body diseases; alpha-synuclein; endocytosis; neurodegeneration

RAB Proteins and Their Regulation

The intracellular system of membrane trafficking is an essential aspect of cell physiology, being at the core of mechanisms for exocytosis, endocytosis, movement, and degradation of cargo within the cell. Ras analog in brain (RAB) GTPases, the largest branch of the Ras-like small GTPase superfamily, are the master regulators of cellular vesicle traffic, with 66 members having been described in humans, 31 in *Drosophila*, and 11 in yeast.[1,2] RAB proteins spatio-temporally regulate membrane docking, tethering, and movements along the cytoskeleton during the various steps of trafficking processes.[3] These processes are driven by their ability to act as molecular switches oscillating from cytosolic inactive-GDP-bound, to membrane-associated active-GTP-bound states.[4] Crucial to the interaction of RAB proteins with membrane vesicles are several key

***Correspondence to:** Dr. D.J. Koss and Dr. T. Outeiro, Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK, NE4 5PL;
E-mail: david.koss@newcastle.ac.uk and E-mail: tiago.outeiro@newcastle.ac.uk

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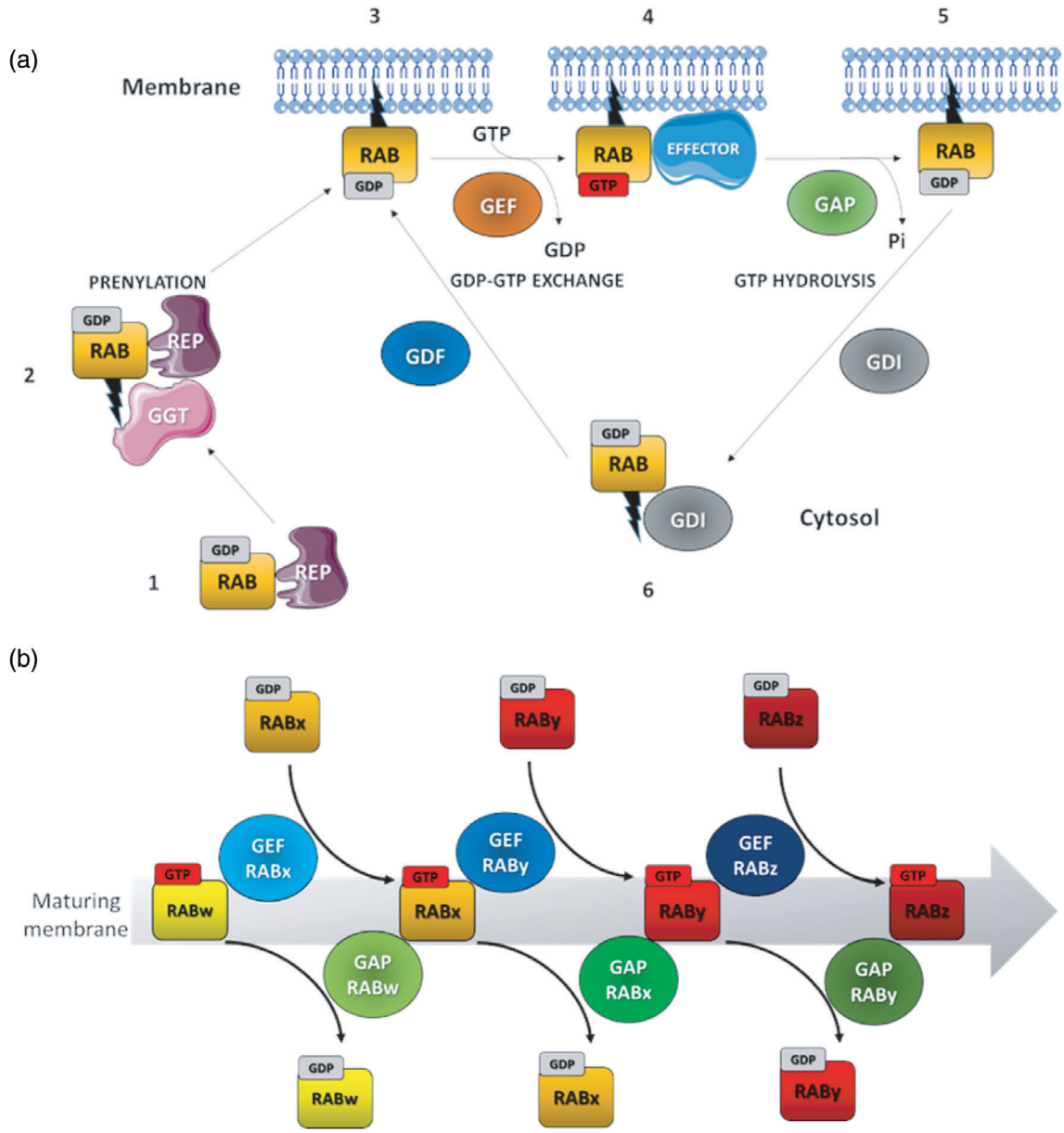

FIG. 1. Ras analog in brain (RAB) regulation. (**A**) RAB protein activation cycle. The newly synthesized RAB, in the GDP-bound inactive form, is recognized by RAB escort protein (REP) (1). REP presents the RAB to a geranylgeranyl transferase (GGT), which geranylgeranylates the RAB on one or two carboxy-terminal Cys residues (prenylation) (2). Prenylation allows the RAB to associate with membranes (3). A guanine nucleotide exchange factor (GEF) catalyzes the exchange of GDP for GTP which activates the RAB. The GTP-bound active RAB associates with multiple effectors (4) and is then converted back to the GDP-bound inactive form by hydrolysis of GTP, which is catalyzed by a GTPase activating protein (GAP) (5). The RAB GDP dissociation inhibitor (GDI) recruits and maintains the GDP-bound RAB in the cytosol (6) until it is removed by a GDI displacement factor (GDF) which allows the RAB to associate with a membrane, restarting the cycle (3). (**B**) RAB protein cascade. During the maturing of a membrane a RAB cascade is achieved with the effectors of each RAB being a GEF for the next RAB and a GAP for the previous RAB. [Color figure can be viewed at wileyonlinelibrary.com]

regulators such as RAB prenylation escort protein (REP), which promotes geranylgeranyltransferase (GGTase)-mediated C-terminus prenylation of newly synthesized RABs (a prerequisite for their association with membranes),[5] and specific membrane-associated guanine nucleotide exchange factors (GEFs), which recruit and activate RABs by promoting the exchange of GDP to GTP. Activated RABs interact with a wide range of effector proteins whose functions include cargo sorting, vesicle formation, movement, tethering, and fusion.[4,6] GTPase activating proteins (GAPs) accelerate the hydrolysis of GTP into GDP and inactivate RABs, which are then extracted from the membrane and chaperoned to the cytosol by a GDP dissociation

inhibitor (GDI), providing a pool of inactive RABs ready to be reutilized.[7] GDI displacement factor (GDF) can subsequently promote GDI release and the RAB activation cycle can recommence (Fig. 1A).

As vesicles mature from one membrane compartment to the next, they associate with different RABs, and the specificity of each RAB can be orchestrated by cascades of RABs, GEFs, and GAPs (Fig. 1B). These RAB cycles are intimately connected with SNARE cycles, thereby regulating the fusion of vesicles with the target organelles/compartments.

Neuronal RABs

Given the highly specialized, dynamic, and polarized nature of neurons it is unsurprising that the maintenance and function of these long-lived cell types critically depend on vesicle transport, exocytosis, and endocytosis.[8-10] Accordingly, several RABs, such as RAB3A and RAB6B, are specifically expressed in the brain, and many other RABs are enriched in the brain.[11] Together these neuron-specific RABs complement non-cell-type-specific RABs in order to orchestrate a variety of critical functions in neuronal homeostasis, such as neurite outgrowth and axon or dendrite formation,[12-14] neurotransmitter release,[15-18] the recycling or degradation of synaptic or endosomal vesicles,[19-29] and synaptic plasticity.[30-35]

Thus, due to the near ubiquitous involvement of RABs in neuronal homeostasis, it is unsurprising that their dysregulation as part of neurodegenerative processes has been widely reported.[9] Nevertheless, the direct association of RAB gene mutations with neuropathy are rare, with the critical exceptions of RAB7A gene mutations associated with Charcot–Marie–Tooth disease type 2B (CMT2B),[36] RAB18 gene mutations with Warburg Micro syndrome,[37] and RAB39B with Parkinson's disease (PD).

Lewy Body Diseases

PD and the related dementia with Lewy bodies (DLB) are pathologically defined by the presence of α-synuclein (aSyn)-rich intraneuronal Lewy bodies (LBs) and are collectively referred to as Lewy body diseases (LBDs). PD is the most common movement disorder and is characterized by resting tremor, bradykinesia, rigidity, and postural instability.[38] The motor features are caused by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, concomitantly with the presentation nigral and brainstem LBs.[39] In contrast, DLB cases exhibit limbic/neocortical predominate LBs and present with visual hallucinations, cognitive fluctuations, rapid eye movement (REM) sleep behavior disorder, and one or more features of PD.[40] Despite the identification of aSyn as the major component of LB pathology, the precise role of these protein inclusions in neurodegeneration remains unclear.

To date, numerous cellular stressors and impairments have associated with neurodegeneration, including oxidative stress, endoplasmic reticulum (ER) stress, DNA damage, mitochondrial dysfunction, and vesicular-mediated protein and lipid trafficking and degradation.[41,42] Strikingly, although most LBD cases are sporadic, around 20 genes are associated with genetically inherited forms of PD including *SNCA* (aSyn), *LRRK2* (leucine-rich repeat kinase2), *VPS35* (vacuolar sortin protein 35), *PINK1* (PTEN-induced putative kinase1), *PARK2/Parkin*, and the subject of this review, *RAB39B*. All proteins encoded by these genes have been implicated in membrane trafficking and/or RAB function[43-45] (see Table 1). Over the last decade, the identification of *RAB39B* mutations as causative in the occurrence of rare early-onset forms of PD has served to further highlight dysfunctional vesicular trafficking as a potential pathogenic source of disease.

RAB39B Mutations and Dysfunction

Originally identified as a mutation locus for X-linked intellectual disability (XLID), the initial study of XLID families reported a likely benign silent *RAB39B* mutation (c.543A > G p.T181T) within the cohort.[95] However, several *RAB39B* mutations were later identified as causative for XLID.[96] Affected families presenting with mild mental impairment and macrocephaly and individual cases demonstrating additional symptoms including autism spectrum disorder and/or seizure occurrence.[96] An association with early-onset PD in addition to XLID was reported in a follow-up study of Australian kindred and a genetically distinct Wisconsin family.[67] In addition to the symptomatic PD presentation, postmortem neuropathological examination of an individual Australian kindred confirmed the presence of cortical and subcortical LBs, neurofibrillary tangles (NFTs), and subcortical atrophy.[67] Similar observations were reported within a member of the Wisconsin family, in which LBs and NFTs were also apparent alongside subcortical atrophy and iron deposition.[97]

To date, a number of *RAB39B* mutations have now been associated with XLID and early-onset PD, the majority of these mutations results in a total loss of RAB39B expression, although examples of reduced protein stability (C.503 > A p.T168K)[67] and altered function (c.574G > A p.G192R)[98] have also been reported (see Table 2 for full details). Interestingly, RAB39B duplication is also linked to XLID, suggesting that tight regulation of RAB39B activity is essential for physiological development. However, there are no reports of PD-like symptomology and neuropathological examination is currently unavailable.[104] Regardless,

TABLE 1 *Familial Parkinson's disease genes and Ras analog in brain (RAB) protein associations*

Genes	Interacting RAB	Functional outcome
aSyn	RAB1A	Overexpression rescues aSyn-induced ER-Golgi traffic defects[46,47]
	RAB3A	Stabilizes aSyn on synaptic membranes; overexpression rescues aSyn toxicity in animal models[46,48-52]
	RAB5A/B	Modulates aSyn clearance and spreading; interacts with mutant aSyn disrupting endocytosis[48,53-58]
	RAB7 RAB8 RAB11A	Modify aSyn clearance and spreading; overexpression rescues aSyn[48,49,55,57,59-66]
	RAB13	Modifies aSyn aggregation, clearance and toxicity[59]
	RAB27A	Modulates secretion of aSyn[62]
	RAB39B	Modulates steady-state levels of aSyn,oligomerization and toxicity[59,67]
LRRK2	RAB3A/B/C/D	LRRK2 kinase substrates[68,69]
	RAB5	Implicated with LRRK2 and Rab11 in *Drosophila* synaptic vesicle recycling[70,71]
	RAB7L1	Phosphorylated by LRRK2. LRRK2 and Rab7L1 interact in the endolysosomal system[70,72-79]
	RAB8A	LRRK2 kinase substrate, interacts with LRRK and RAB7L1 in endosomal homeostasis. LRRK2-mediated phosphorylation of RAB8A leads to centrosomal alterations[68,78,80-82]
	RAB10	LRRK2 kinase substrate, involved with LRRK and RAB7L1 in endosomal homeostasis[68,78,80-82]
	RAB12	LRRK2 kinase substrate[68]
	RAB32	Directly interacts with LRKK and is linked to SNX6/retromer trafficking at the Golgi[83,84]
	RAB35	LRRK2 kinase substrate[68]
	RAB43	LRRK2 kinase substrate[68]
VPS35	RAB5	Implicated with VPS35, LRRK, and Rab11 in *Drosophila* synaptic vesicle endocytosis[71]
	RAB7	Recruits retromer on endosomes via interactions with the Vps sub-complex[85-87]
	RAB7L1	Indication of functional relationship between LRRK, RAB7L1, and VPS35[72]
PINK1	RAB8A/B	PINK1-induced phosphorylation alters the ability of RAB8A to interact with its GEF Rabin8[88-90]
	RAB13	Phosphorylated after PINK1 activation[88]
PARKIN	RAB5	Recruited to damaged mitochondria after Parkin-mediated ubiquitination of RABGEF1[91]
	RAB7A	Recruited to damaged mitochondria after Parkin-mediated ubiquitination of RABGEF1. Parkin also regulates the activity of Rab7 in the endo-lysosomal pathway[91-94]

Common familial Parkinson disease (PD) genes, alpha-synuclein (aSyn), leucine-rich repeat kinase 2 (LRRK2), vacuolar protein sorting-associated protein 35 (VSP35), PTEN-induced kinase (PINK1) and PARKIN are listed alongside their associated RAB proteins and functional outcome.
Abbreviations: RAB, Ras analog in brain; ER, endoplasmic reticulum; GEF, guanine nucleotide exchange factor.

despite the identification of a number of XLID- and LBD-affected families which carry *RAB39B* mutations, large-scale studies of LBD cohorts have failed to find significant prevalence among Caucasian or Asian populations.[105-108] Thus, *RAB39B* mutations are likely rare and do not seem to contribute to the occurrence of LBD outwith XLID cases. However, the symptomatic and pathological recapitulation of LBDs following the loss of RAB39B clearly highlights the protein's functions as critical for neuronal viability and for aSyn homeostasis. Consequently, alterations in RAB39B may still contribute to the pathogenesis of LBDs in the wider population. Indeed, ourselves and others have recently reported on the loss and/or redistribution of RAB39B in idiopathic LBD variants.[97,109]

RAB39B and Endosomal Trafficking

The human *RAB39B* gene, identified in 2002, encodes for a protein with 74.2% homology with RAB39A.[110] Phylogenetic analysis and subfamily segregation suggests that in addition to RAB39A, RAB39B is also closely related to RAB 2, 4,11A/B, and 25, each of which are involved in the trafficking of endosomes.[111,112]

TABLE 2 *RAB39B gene mutations, symptomology, and neuropathology*

Mutations	Molecular consequence	Symptomology	Pathology
c.21C > A p.Y7X	Nonsense mutation/loss of expression	Mental impairment/autism/ seizures	Macrocephaly[96]
c.215 + 1G > A	Intronic mutation/loss of expression	Mental impairment/autism/ seizures	Macrocephaly[96]
45 kb deletion	Gene deletion/loss of expression	Mental impairment (non-progressive)PD symptomology/onset ~45 years of age	Macrocephaly Crt and SCrt LBs/NFTs Iron deposition[67]
C.503C > A p.T168K	Missense mutation Reduce stability/loss of expression	Mental impairment (non-progressive) /seizuresPD symptomology /onset ~20 years of age	Macrocephaly Crt and SCrt LBs/NFTs Iron deposition SCrt atrophy[67]
c.557G > A p.T186X	Nonsense mutation /loss of expression	Mild mental impairment (non-progressive)PD symptomology/onset~39 years oldExecutive function deficits and mood disorder	NR[99]
c.574G > A p.G192R	Missense mutation Impaired membrane association and function	Mild mental impairment (non-progressive) PD symptomology/onset ~50 years of age	NR[98]
c.428C > G p.A143G	Missense mutation	PD symptomology/onset 47 years of age	NR[98]
c.624_626delGAG p.R209del	Deletion mutation	PD symptomology/onset 67 years of age	NR[98]
c.432delA pT145Tfs*3	Deletion mutation/loss of expression	Mental impairmentPD symptomology/onset 29 years of age	Abnormal DAT and SPECT signals Iron deposition[100]
c.123G > T p.V41V	Silent mutation In silico cryptic splice site determined	Normal intellectual capacityPD symptomology/onset 45 years of age	NR[100]
c.536dupA p.I180Afs*48	Duplication mutation/loss of expression	Mental impairmentPD symptomology/onset ~12 years of age	GP atrophyBG calcification[101]
c.137dupT p.S47L.fs*44	Duplication mutation/loss of expression	Mental impairment PD symptomology/onset ~60 years of ageExecutive function deficits and mood disorders	Abnormal SPECT signalSN and GP atrophyBG calcification[102]
c.371delA p.K124S.fs*10	Deletion mutation/loss of expression	Mental impairmentPD symptomology/onset ~44 years of ageExecutive function deficits and mood disorders	Abnormal SPECT signalSN and GP atrophy[102]
c.559G > T p.E187X	Missense mutation	Mental impairment/autism Motor impairment/tremor	NR[103]
0.5 Mb dul Xq28	Duplication of RAB39B and 7 other genes	Mental impairment	NR[104]

Mutations are cited as per changes in codon (c.) and protein amino acid sequence, mutations resulting in frameshifts (fs) and position of induced stop codon (*) are also indicated. Molecular consequences, generalized symptomology, and onset age of Parkinson's disease symptoms are provided.
Abbreviations: Crt, cortical; sCrt, subcortical; PD, Parkinson's disease; LB, Lewy body; NFT, neurofibrillary tangle; NR, not reported; DAT, dopamine transporter; SPECT, single photon emission computed tomography; GP, globus pallidus; BG, basal ganglia; SN, substantia nigra.

Despite its assignment to a group of endosomal trafficking RABs, little is definitively understood about the exact function of RAB39B in this process. At a conceptual level the endosomal system regulates the fate of endocytosed cargo, which is initially sorted in early endosomes, from which the internalized proteins are trafficked for either degradation in late endosomes, ultimately entering lysosomal pathways, or are sorted for the return to the plasma membrane via exocytosis. The process of exocytosis can be further spilt into either a direct rapid route (endosomes to plasma membrane) or via slow endocytic recycling compartments at times also involving retrograde transport from the endosomes to the Golgi apparatus.[113]

In both mice and humans RAB39B is highly enriched in brain neurons and is developmentally upregulated after birth, with expression being highest within the hippocampus, neocortex, and substantia nigra.[96,97] When expressed in various cell types including in primary hippocampal neurons, RAB39B colocalizes with VAMP4 and syntaxin 16, markers of retrograde Golgi trafficking, as well as with ER, Golgi, ER-Golgi trafficking markers, but also in early endosomes and within slow endosomal recycling and post-Golgi secretory pathways where it partially colocalizes with RAB11.[67,96] The mediation of endocytotic recycling via RAB39B is further supported by its association with myosin Va, a post-Golgi actin-based motor protein,[114] as well as its partial colocalization with trans-Golgi network (TGN) protein p230, known to influence transport from the TGN to the plasma membrane.[67] Recently, RAB39B has also been localized with ER and ER-Golgi trafficking markers.[115] Collectively, these studies implicate RAB39B in a variety of trafficking events predominately associated with endocytotic retrograde and/or early-stage anterograde secretory transport (Fig. 2A). Therefore, alterations in RAB39B function likely have widespread consequences for cellular trafficking and without further investigation the predominant consequences for neuronal homeostasis as a result of disrupted vesicle trafficking are difficult to discern. Nevertheless, a number of key studies have begun to shed light on this.

RAB39B and Neurite Elongation and Synaptic Development

At a subcellular level, RAB39B is enriched in the growth cones (GCs) of developing neurites. Intriguingly, both knockdown and overexpression of RAB39B results in a reduction in GC number and in neurite length.[96,104] This impaired neuritic outgrowth likely contributes to the reduced number of presynaptic terminals also observed following the modulation of RAB39B expression.[96,104] Such deficits may relate to the improper regulation of membrane remodeling at the GC leading edge, as efficient endosomal recycling is required for removal and insertion of guidance and adhesion-based receptors and lipids.[116,117] Although the exact mechanism for this disruption of neuronal maturation has not been established, such impaired neurite outgrowth and pathfinding likely contribute to the developmental abnormalities seen in those carrying loss of function mutations within the *RAB39B* gene.

RAB39B and Glutamatergic Receptor Maturation/Modulation

RAB39B also affects the maturation of AMPA receptors (AMPAR) subunits, a process that involves a change from the predominantly Ca^{2+}-permeable GluA1 AMPAR subunits to include Ca^{2+}-impermeable GluA2-3 subunits,[118] thereby promoting the adoption of the classical Na^{+}-based electrochemical signalling of AMPARs. Knockdown of RAB39B in neurons results in the accumulation of GluA2 and GluA3 subunits within the cell body, which fail to traffic into the dendrites, ultimately reducing their surface expression and altering AMPAR-mediated postsynaptic currents.[119] In this context, RAB39B appears to interact with protein interacting with C kinase (PICK1), which itself associates with GluA2 within the ER and mediates the trafficking of GluA2 subunits through the Golgi and into an early secretory pathway. In contrast, studies focused on a known GEF for RAB39B, C9orf72, have found that following C9orf72 knockout, a loss of postsynaptic RAB39B is observed alongside a corresponding increase in GluA1 postsynaptic localization without change in GluA2 levels.[120]

Independent of the finer details of which subunits are altered, the loss of AMPAR regulation likely has widespread functional consequences. Such changes may be of particular relevance for neurodegeneration as both outcomes favor an increase in Ca^{2+} permeability and thus may increase vulnerability to excitotoxic events.[121] The altered complement of AMPAR subunit expression is consistent with the histopathological study of the cortical expression of these receptors in LBD.[122] Therefore loss of RAB39B function, either as a consequence of gene mutation or pathological disruption (as discussed below), may contribute to changes in AMPA receptor subunit composition and to a progressive increase in neuronal vulnerability towards Ca^{2+}-mediated degenerative insults, thought to participate in the cell death associated with LBDs.[123] Despite the findings of these in vitro-based investigations, a recent study of *RAB39B* gene knockout mice has observed a reduction of postsynaptic NMDA receptor subunits as oppose to AMPA receptors, suggesting that in vivo deficits in synaptic function may differ from those established within in vitro models.[124]

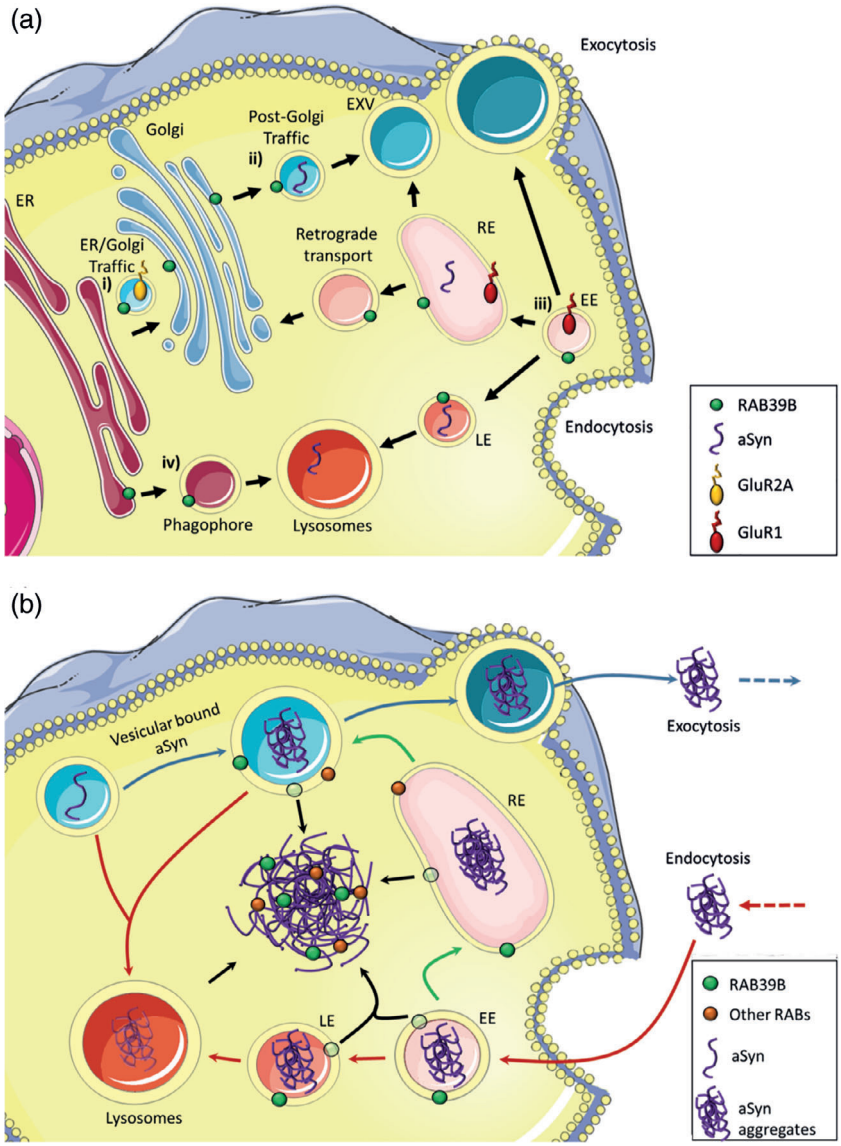

FIG. 2. RAB39B-mediated vesicular transport and site of interaction with alpha-synuclein (aSyn) homeostasis. (**A**) Vesicular localization of RAB39B, based on colocalization studies, is indicated alongside key proteins impacted by RAB39B impairments. RAB39B mediates trafficking from the endoplasmic reticulum (ER) to Golgi, influences GluA2 surface expression (i). Localization of RAB39B within the early secretory vesicle, where it may colocalize with membrane-bound aSyn (ii). RAB39B-mediated regulation of endosomal trafficking, localized to early endosomes (EE) and recycling endosomes (RE) alongside internalized GluA1 subunits and aSyn (iii). The association of RAB39B within late endosomes (LE) which feed into lysosomes, generated from RAB39B-positive phagophores is shown alongside its potential to influence aSyn degradation (iv). (**B**) Sites of interaction between a loss of RAB39B function and aSyn accumulation and aggregation. Exocytotic release pathway via vesicular-bound aSyn and endocytotic trafficking of aggregate-prone aSyn via EE and ER towards re-release and via LE to the lysosomal degradation is shown. A loss of RAB39B at each point in the processing pathway (indicated via transparent ball) may lead to increased aSyn retention, accumulation, and aggregation. The disruption of this pathway independent from a loss of function mutation within the RAB39B gene may trigger the deposition of aSyn, in turn trapping key trafficking proteins inclusive of RAB39B, further impeding the homeostatic clearance of aSyn.

RAB39B and Autophagy

RAB39B may also participate in the formation of autophagosomes from the ER membrane. Defects in autophagy due to loss of C9orf72 can be rescued by the expression of constitutively active RAB39B, but not other RABs.[125] Consistently, endogenous RAB39B colocalizes with the lysosomal marker LAMP1,[67] and when overexpressed RAB39B associates with a member of the phosphatidylinositol 3-kinases (PI3Ks) complex initiator of autophagosome formation, Beclin 1.[126] However, when investigated at endogenous levels the association of RAB39B with Beclin 1[127] and the localization of RAB39B with LAMP1[115] has not been replicated. Nevertheless, in *RAB39B* gene knockout mice and in responses to the downregulation of *RAB39B*

gene expression in mouse N2A cells a reduction in autophagolysosome formation has been observed, suggesting decreased autophagic flux.[124] When autophagy was induced with rapamycin, this impairment was eliminated, indicating that a loss of RAB39B expression impairs basal autophagy, but not autophagy induction. Notably, rapamycin treatment improved defects in synaptic plasticity and memory observed in *RAB39B* gene knockout mice, suggesting that autophagy plays a central role in phenotypes observed with RAB39B deficiency.[124]

Regulation of aSyn Homeostasis Via RAB39B

Of clear relevance to the association of RAB39B with PD is the potential of the protein to modulate intracellular levels of aSyn. Initial studies suggested that the experimental knockdown of RAB39B resulted in an overall reduction in steady-state levels of aSyn in primary neuronal preparations.[67] Yet, in contrast, in neuroglioma cells, a reduction of RAB39B expression facilitated aSyn oligomerization and aggregation and was associated with increased cellular toxicity.[59] As the former finding is contrary to the accumulation of aSyn observed in human postmortem studies, it may be that this contradiction is a consequence of interactions between the role of RAB39B in synaptic development and that of a direct interaction with aSyn homeostasis. Indeed, during development an absence of RAB39B may perturb the development and maturation of synapses, resulting in a reduction of several synaptic proteins required for normal function, including aSyn, whilst beyond the developmental period, the same absence of RAB39B may promote the cellular retention of aSyn and its aggregation.

Although the mechanisms by which a loss of RAB39B leads to the dyshomeostasis of aSyn is unknown, the disruption of autophagic clearance has recently been proposed as central to this, in line with the impairments seen following the expression of mutations within the RAB39B GEF C9orf72[128] and would appear to be supported by the autophagy deficits in RAB39B knockout mice.[124] Whilst such a proposition is interesting it remains unclear why such generalized failure of lysosomal clearance would preferentially lead to the accumulation and aggregation of aSyn over other aggregate prone proteins, and indeed several studies have failed to find an impact upon lysosomal degradation following the loss of RAB39B.[126,127] Equally, it must also be considered that Lewy pathology is not commonly reported in cases of amyotrophic lateral sclerosis and frontotemporal disease associated with the loss of function hexanucleotide repeat expansion of the c9orf72 gene[129] and thus such a close relationship between the mode of cellular dysfunction induced by a loss of RAB39B activity and the loss of c9orf72 activity would seem unlikely. Nevertheless, rare cases of PD linked to c9orf72 mutation have been reported,[130] perhaps indicative of a partial overlap in defective pathways, with innate or environmental factors modifying the cellular outcome to one more closely aligned with those mediated by the loss of RAB39B.

Here, we would propose that the function of RAB39B relates not only to autophagy but also to endosomal trafficking particularly within retrograde trafficking vesicles, early and late endosomes endosomes,[67] and recycling endosomes where it colocalizes with RAB11.[96] Thus, akin to other PD-associated mutations within endosomal trafficking regulators such as the retrograde trafficking protein VPS35,[131,132] the early endosomal-associated DNAJ13[133] and the RAB-regulating LRRK2,[68] the loss of RAB39B may perturb essential endosomal trafficking of aSyn which in addition to compromised autophagic clearance leads to its aggregation.

Such a model would suggest that the compromised endosomal pathways are likely to impact upon several different pools of aSyn including the significant portion of the aSyn which is processed for extracellular release either through exosomal and/or exocytotic pathways.[134] In neurons, vesicles containing intralumenal aSyn are released via an atypical ER-Golgi-independent exocytosis pathway, in a process which is intimately linked with lysosomal degradation rates.[135,136] Rather critically, vesicular aSyn has a greater propensity for aggregation compared to aSyn within the cytoplasm,[135,137] suggesting that the rapid processing of vesicular-bound aSyn is of high importance to minimize the potential for aSyn deposition. Although the exact regulation of aSyn exocytosis remains to be resolved, it is known that the process requires the activity of the RAB11a,[135,137] which is both spatially[96] and functional[111,112] related to RAB39B.

The endosomal transport of aSyn is not only relevant to the regulation of de novo synthesized aSyn but also to the extracellular pools of aSyn, particularly oligomeric and aggregates species, which enter cells via a variety of internalization processes.[134] Internalized aSyn oligomers and aggregates rapidly enter endosomal pathways colocalizing with early and late endosomal markers and are largely trafficked into the lysosomes for degradation.[138,139] However, again, a significant proportion of the internalized aSyn can also be recycled back into the extracellular environment, utilizing a similar RAB11-dependent atypical ER-Golgi-independent pathway as employed for the release of intracellularly produced aSyn.[60]

Thus, efficient endosomal trafficking of both endogenous and exogenous aSyn pools would appear as critical not only to the regulation of total intracellular aSyn

abundance but also in the clearance of aggregation-prone aSyn species. Moreover, these studies highlight aSyn endosomal trafficking as a major potential site of dysfunction, which may underlie the association of RAB39B mutations and aSyn aggregation.

Whilst the exact point of dysfunction within the endosomal pathway induced by an absence of RAB39 is unknown, be that in early, recycling, or retrograde endosomes or indeed in the regulation of autophagy, it is noteworthy that the axonal and synaptic expression of RAB39B[96,120] is in line with reports of the initial sites of aSyn aggregate formation within these subcellular compartments proceeding their trafficking and maturation into somatic LBs.[140-143] Thus, in the absence of a key regulator of endosomal trafficking, such as RAB39B, the entrance of vesicle-bound aSyn into either degradation or exocytosis pathways may stall, with the prolonged retention of aSyn leading to aggregation and deposition. Likewise, in accordance with several studies reporting the disruption of endosomal trafficking following aSyn overexpression,[46,144,145] should the abundance of vesicular-bound aSyn exceed the endosomal handling capacity of the cell, blockage and aggregation within the pathway may ensue. The impact of such initial deposition of aSyn with endosomal vesicles to cellular homeostasis would be two-fold, as in addition to the formation of toxic aSyn species, the formation of Lewy pathology around cargo-bearing vesicles may entrap a variety of essential lipids and proteins including RAB proteins themselves, further propagating intracellular aggregation (Fig. 2B). This secondary consequence of vesicular aggregation formation is consistent with our previous observation of sequestration of RAB11a and RAB13 in cellular models of aSyn deposition as well as the coaggregation of RAB39B in a subpopulation of LBs in idiopathic DLB cases,[109] which together implicate the dysfunction of key RAB proteins for both familial cases of LBD and idiopathic variants. Furthermore, should a loss of functional RAB39B be mediated by its inclusion within LBs, affected neurons maybe further impacted by downstream alterations of synaptic homeostasis as a consequence of altered glutamatergic signalling and autophagic deficits.

Pharmacological Targeting of RAB Proteins

Although it must be acknowledged that the direct targeting of RAB39B activity in those carrying XLID-associated loss of function mutations would be fruitless, there may be sufficient functional overlap in the system such that the targeting of closely related RAB proteins such as RAB11 may be a beneficial line of investigation. Furthermore, the above outlined potential of a wider relevancy for targeting RAB proteins, RAB39B, and others in idiopathic cases has prompted a clear interest in identifying therapeutic strategies aimed at their modulation.

Conceptually, a number of interaction sites for targeting RAB proteins exist including RAB prenylation, either acting at the C-terminus of the RAB protein itself or at the GGTase enzyme to regulate membrane interactions, the modulation of RAB activation either at the point of GTP binding, or in the expression and colocalization of GEFs, GAPs, and GDIs or indeed via the expression and turnover of RAB proteins themselves.[146] Nevertheless, targeting RAB proteins is in general challenging due to the high sequence homology amongst GTPase families and the strong affinity of small GTPase for GTP (~pM), largely negating attempts for competitive nucleotide antagonism. To date, the majority of efforts have been focused on reducing the activation of RABs in line with their overactivation in cancer.[147] This work has led to a number of promising, albeit rather non-specific, compounds such as the broad-spectrum GTPases inhibitor CID1067700[148] and several GGTases inhibitors such as psoromic acid[149] and 3-(3-pyridyl)-2-hydroxy-2-phosphonopropanoic acid.[150] Despite the potential for improved specificity to be gained from targeting GEF, GAPs, and GDIs, relatively little success has been achieved in this respect; however, their continued characterization may yet offer the best opportunities for the development of small molecules targeting RAB activity.[4,151] Such approaches have proven fruitful at least within the related Ras GTPase families, with Ras GEF inhibitors NSC-658497 against SOS1[152]and NPPD against TRIO-GEF1D,[153] as well as an inhibitor of the Rho GAP, male germ cell Rac GAP known as MINC1[154] having been established. In this respect the identification of a number of RAB39B GEFs such as C9orf72[155] and DENN domain (DENND) proteins DENND5A/B[156] and GAPs such as TBC1D18/RABGAP1L and RUTBC3[157,158] may prove advantageous in the search for pharmacological targets.

In parallel, progress in identifying allosteric sites and modulators of RAB proteins is also being made.[159] High-throughput screens have identified promising RAB activators, these derivatives of salicylic, indole, and nicotinic acid stabilize the GTP-bound structure of RAB2 and RAB7, independent of associated GEF and GAP, yet lack robust specificity also activating Ras and other Ras-related GTPases.[160] Nevertheless, this recent progress rebukes the former "undruggable" status of GTPases and the emerging compounds may serve as the basis for future improved drug development. Despite much work still being required to elucidate any potential mechanisms of direct pharmacological interventions, several drugs have been identified to modulate downstream pathways affected by RAB gene mutations.[146] For example, the treatment of neuroblastoma

cells expressing CMT2B mutant RAB7 genes with valproic acid can overcome deficient neurite outgrowth via readdressing disruptions to C-Jun N-terminal kinase pathways.[161] Furthermore, the targeting of cholesterol to the plasma membrane can overcome the RAB11-mediated deficit in cholesterol esterification within Niemann–Pick type C1 fibroblasts.[162] Thus, the targeting of RABs directly or correcting impacted RAB functions may prove beneficial in the further treatment of neurodegenerative conditions.

In this regard, it is of relevance that in striatal neurons, the orphan G-protein-coupled receptor 52 (GRP52) was found to enhance HTT toxicity via the activation of a RAB39B GEF, acting in opposition to the Rabgap1l GAP which is epistatically expressed in relation to GPR52.[163] The identification of a regulatory receptor capable of mediating changes in the activity of RAB39B clearly holds potential for the development of relevant agonists or antagonists in order to readdress alterations in RAB39B activity. Nevertheless, given the potential for enhanced toxicity of some neurodegenerative proteins, careful consideration following extensive investigation will have to be conducted when seeking to modulate levels/activity of this protein within the aging brain.

Outlook

Clearly much remains to be determined about the intricacies of intracellular trafficking routes and how neurons utilize such pathways for the regulation and clearance of aSyn. Whilst genetic associations place RAB39B at the centre of aSyn dysfunction and thus LB deposition, the specific point of interaction between the two is not currently determined. Future research focused on the uptake, transport, and release of vesicular-bound aSyn following the manipulation of RAB39B activity is now required to further delineate the consequences of aSyn retention and aggregation. Moreover, studies investigating the potential for compensation and recovery of this system via the augmented activation of related RAB proteins may serve to validate various therapeutic strategies.

Similarly, should RAB39B prove a viable future target, establishing the route of clearance and thus the fate of RAB39B trafficked aSyn should be considered of high importance and will likely further inform potential therapeutic approaches. For example, whilst current studies focused on the health of individual cells would appear to support a protective role for RAB39B-mediated trafficking in the clearance of intracellular aSyn, caution must be exercised, as if RAB39B functions serve to facilitate the extracellular release of aSyn as opposed to its ultimate degradation, its further activation may augment prion-like spread of pathology and thus be detrimental in the context of the whole brain as opposed to that of a single cell. Despite the low frequency of RAB39B mutations within the human population and the confounding XLID presentation of carriers, the recent observations made by ourselves and others of a disruption of RAB39B subcellular distribution and also of its sequestration in LBs in idiopathic cases of LBD,[97,109] further strengthens the need to clarify the relationship between RAB39B and aSyn and indeed its role in the formation of concomitant disease-modifying pathologies.

In the absence of mutations within its gene and/or the genes of its effectors, it is unknown how RAB39B may contribute to the development of age-related neurodegeneration onset. It is plausible that declining RAB39B levels or activation in line with age may lead to intercellular trafficking becoming vulnerable to disruption. This aging-related decline in RAB39B may in turn sensitize neurons towards previously subthreshold stressors, inclusive of familial and risk gene mutations which summate to impact upon vesicular trafficking and consequently facilitate the accumulation and aggregation of aSyn. Critically, whist indeed some key endocytosis proteins are increased in their expression with age,[164-166] a detailed profile of how the expression of each RAB protein and its modulators (GEFs/GAPs, etc.) alters over the course of human aging is as yet undefined. Thus, the extent to which such an age-induced vulnerability contributes to a tipping point of aggregation and cellular dysfunction is uncertain. Nevertheless continued research into the functional roles of RAB39B in protein and lipid trafficking will serve to clarify its significance in cellular development, homeostasis, and in the pathology of LBDs and other neurodegenerative diseases. ■

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