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Review

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Roles of Rab GTPases in glial function and neurodegeneration

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Abstract: Neurodegenerative diseases, such as Alzheimer's Disease (AD), Parkinson's Disease (PD), and Multiple Sclerosis (MS), pose severe threats to human health. Dysfunction of the central-nervous-system (CNS) glial cells—including astrocytes, oligodendrocytes, and microglia—contributes to the pathogenesis of neurodegenerative diseases. Rab GTPases, the largest branch of the Ras superfamily, are key spatiotemporal regulators of cellular trafficking via cycling between guanosine triphosphate (GTP)- and guanosine diphosphate (GDP)-bound states. Accumulating evidence indicates that small Rab GTPases play a critical role in glial-cell homeostasis and in the pathogenesis of neurodegenerative disease. This review summarizes current findings on the function of Rab GTPases in the three major CNS glial cell types. It emphasizes how Rab GTPases orchestrate key processes including cellular homeostasis, phagocytosis, exocytosis, and myelin formation. Given the established link between glial dysfunction and neurodegeneration, a comprehensive understanding of the functions of Rab GTPases in glial cells offers critical insights for identifying novel therapeutic interventions.

Key words: Rab GTPase; Astrocyte; Oligodendrocyte; Microglia; Neurodegenerative disease

1 Introduction

Neurodegenerative disorders are emerging as a severe global health challenge. However, no curative therapies are currently available (Mittal et al., 2023; Collaborators, 2024). Although neuronal damage and loss are hallmark features of neurodegenerative disease (Mittal, et al., 2023) and have long been the primary focus, it has become increasingly recognized that CNS glial cells (astrocytes, oligodendrocytes, and microglia) play a significant role (Gao et al., 2023; Temple, 2023; Stoklund Dittlau and Freude, 2024). Microglia perform continuous surveillance of the brain's microenvironment, protecting neurons through phagocytosis of misfolded proteins, cellular debris, and dead cells (Cserep et al., 2020). Astrocytes, in turn, are crucial for the integrity and function of the neuronal network, as they form tripartite synapses with neurons and thereby orchestrate synaptic activity modulation and neurotransmitter recycling (Verkhratsky and Nedergaard, 2018). Furthermore, oligodendrocytes facilitate rapid, saltatory conduction of action potentials by insulating axons with a lipid-rich myelin sheath (Simons and Nave, 2015). Given these vital functions, dysfunction across these glial cell types constitutes a common pathological basis for numerous neurological disorders, including AD, PD, and MS (Kwon and Koh, 2020).

Rab GTPases, the largest subgroup within the Ras superfamily, comprise more than 60 discrete members encoded in the human genome (Klopper et al., 2012). Through prenylation modifications—typically the

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addition of geranylgeranyl groups to cysteine residues at the C-terminus—Rab GTPases localize to specific organelles or vesicles (Leung et al., 2006). Functioning as molecular switches, they precisely coordinate the key stages of vesicular trafficking—including budding, motility, tethering, and fusion—thereby governing essential processes such as endocytosis, cargo transport, secretion, and degradation (Hutagalung and Novick, 2011; Zhen and Stenmark, 2015). Consequently, aberrant regulation of Rab GTPase-mediated trafficking has been strongly implicated in the pathogenesis of a range of human diseases, notably neurodegenerative disorders. Mutations in *RAB39B and RAB32* have been found in patients with early-onset and autosomal-dominant Parkinson's disease, respectively (Wilson et al., 2014; Lesage et al., 2015; Mata et al., 2015; Shi et al., 2016; Gustavsson et al., 2024; Monfrini et al., 2024). Meanwhile, *RAB7A* mutations have been linked to Charcot-Marie-Tooth disease type 2B (Colecchia et al., 2018; Romano et al., 2022).

Although Rab GTPases have traditionally been studied in the context of neuronal function, their essential and multifaceted roles in glial cells are now increasingly recognized (Ng and Tang, 2008; Wu et al., 2021). This review examines how dysregulation of these specific Rab-mediated processes — such as impaired microglial receptor recycling and chemotactic migration; defective astrocytic neurotransmitter clearance and membrane remodeling; and disrupted delivery of myelin proteins in oligodendrocytes—triggers a cascade of neuroinflammation, homeostatic failure, and demyelination, ultimately contributing to the progression of neurodegenerative disease.

2 Function of Rab GTPases in microglia

2.1 Rab GTPases regulate microglial inflammatory signaling via recycling of TLR4 and TfR

Using an oxygen-glucose deprivation/reoxygenation (OGD/R) model to mimic ischemic injury in vitro, Song et al. reported that Rab1a in HMC3 human microglial cells promotes anterograde trafficking of Toll-like receptor 4 (TLR4) to the plasma membrane, enhancing its surface presentation and responsiveness to ligands like lipopolysaccharide (LPS) and thereby amplifying pro-inflammatory cytokine expression. Conversely, Rab1a knockdown has been shown to attenuate the microglial inflammatory response by inhibiting the TLR4/ Nuclear factor-kappa B (NF-κB) signaling pathway (Song et al., 2020). Beyond Rab1a-mediated TLR4 trafficking, Rab8a orchestrates receptor recycling by regulating the movement of tubular vesicles along microtubules (Sharma et al., 2009; Kobayashi et al., 2014). Under pro-inflammatory conditions, Rab8a is recruited to lysosomes and phosphorylated by leucine-rich repeat kinase 2 (LRRK2). This modification impedes its activation by the guanine nucleotide exchange factor (GEF) Rabin8, leading to disrupted transferrin receptor (TfR) recycling, intracellular iron accumulation, and microglia-driven neurotoxicity (Mamais et al., 2021).

2.2 Rab GTPases orchestrate microglial chemotaxis

The small GTPase Rab27a is a key regulator of secretory lysosome and exosome release (Ostrowski et al., 2010). Its critical function in the nervous system was demonstrated by Dou et al., who showed that Rab27a is essential for long-distance, adenosine triphosphate (ATP)-directed migration of microglia toward injury sites (Davalos et al., 2005; Dou et al., 2012). This process is mediated by Rab27a-dependent lysosomal exocytosis, which releases ATP to establish a crucial chemotactic gradient, thereby guiding microglia to sites of damage or inflammation.

Beyond its canonical roles in Golgi-to-plasma membrane trafficking, endosomal recycling, and autophagy (Liu and Grant, 2015; Li et al., 2016; Etoh and Fukuda, 2019), Rab10 exhibits divergent, cell-type-specific roles in the CNS. While its elevated phosphorylation exacerbates pathology in neurons (Ridge et al., 2017; Yan et al., 2018; Singh et al., 2023), Rab10 and its phosphorylated form at Thr73 (pRab10-T73) promote microglial phagocytic activity that may contribute to neuroprotective effects on neurons. Phosphorylation of Rab10 prevents its interaction with EH domain binding protein 1 like 1 (EHBP1L1), which consequently inhibits membrane scission and tubular-vesicle transport by blocking the recruitment of amphiphysin 1/bridging integrator 1 (Amph1/Bin1) and dynamin, respectively (Nakajo et al., 2016). This results in

endosomal sequestration of receptors like C-C chemokine receptor 5 (CCR5), cluster of differentiation 11b (CD11b), and major histocompatibility complex II (MHCII). The accumulated endosomes form a signaling platform that promotes protein kinase B (Akt) activation and amplifies CCL5-induced chemotaxis, enabling phagocytes to migrate to injury sites and execute anti-inflammatory and phagocytic functions (Liu et al., 2020).

2.3 Rab GTPases coordinate microglial exosome-mediated intercellular communication

Like other cell types, microglia employ exosomes for intercellular communication (Ji et al., 2024). Mechanistically, Rab GTPases facilitate exosome secretion by promoting the tethering and docking of multivesicular bodies (MVBs), with the final fusion step being calcium-dependent (Savina et al., 2002; Savina et al., 2005). This process is regulated by Rab GTPases, including Rab11 and Rab27. Kumar et al. demonstrated that cocaine disrupts this pathway by downregulating the expression of Rab11 and Rab27 in microglia, thereby reducing production of exosomes and altering their cargo (Kumar et al., 2021). This dysregulation impairs intercellular communication and could potentially contribute to cocaine-induced microglial activation (Chivero et al., 2021).

2.4 Rab7 regulates microglial oAβ clearance

Rab7 governs the transport, maturation, and fusion of endosomes with lysosomes. In microglia, high concentrations of oligomeric amyloid-β (oAβ) disrupt the Rab5-to-Rab7 conversion, impairing endosomal maturation and lysosomal clearance of oAβ (Yao et al., 2019). The ensuing accumulation of oAβ further damages lysosomal membranes, triggering a compensatory upregulation of the GTPase-activating protein (GAP) TBC1 domain family member 15 (TBC1D15), which enhances level of dynamin2 to promote membrane repair. Meanwhile, in its role as a GAP, TBC1D15 also inactivates Rab7. This inactivation prevents autophagosome–lysosome fusion, ultimately creating a vicious cycle by reducing Aβ clearance capacity and thereby accelerating the progression of neurodegenerative disease (Wu et al., 2024).

2.5 Rab27a/b regulate microglial redox homeostasis

In microglia, the small GTPases Rab27a and Rab27b serve as pivotal regulators of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase trafficking and localization, thereby determining whether the enzyme complex docks at phagosomal membranes or the plasma membrane. Rab27a primarily functions as a negative regulator by "anchoring" secretory vesicles to the cortical actin cytoskeleton through the myosin VIIA and Rab interacting protein (MyRIP)–filamentous actin (F-actin) network, effectively applying a braking mechanism that restricts premature vesicle fusion and uncontrolled oxidase release. In contrast, Rab27b facilitates the transition of vesicular transport from microtubule-based to actin-based motility, thereby orchestrating the precise spatiotemporal dynamics of reactive-oxygen-species production. Through these complementary actions, Rab27a and Rab27b collectively fine-tune the magnitude and spatial distribution of microglial superoxide production by modulating compartmentalization of the NADPH oxidase complex in a stimulus-dependent manner (Ejlerskov et al., 2012; Fukuda, 2013).

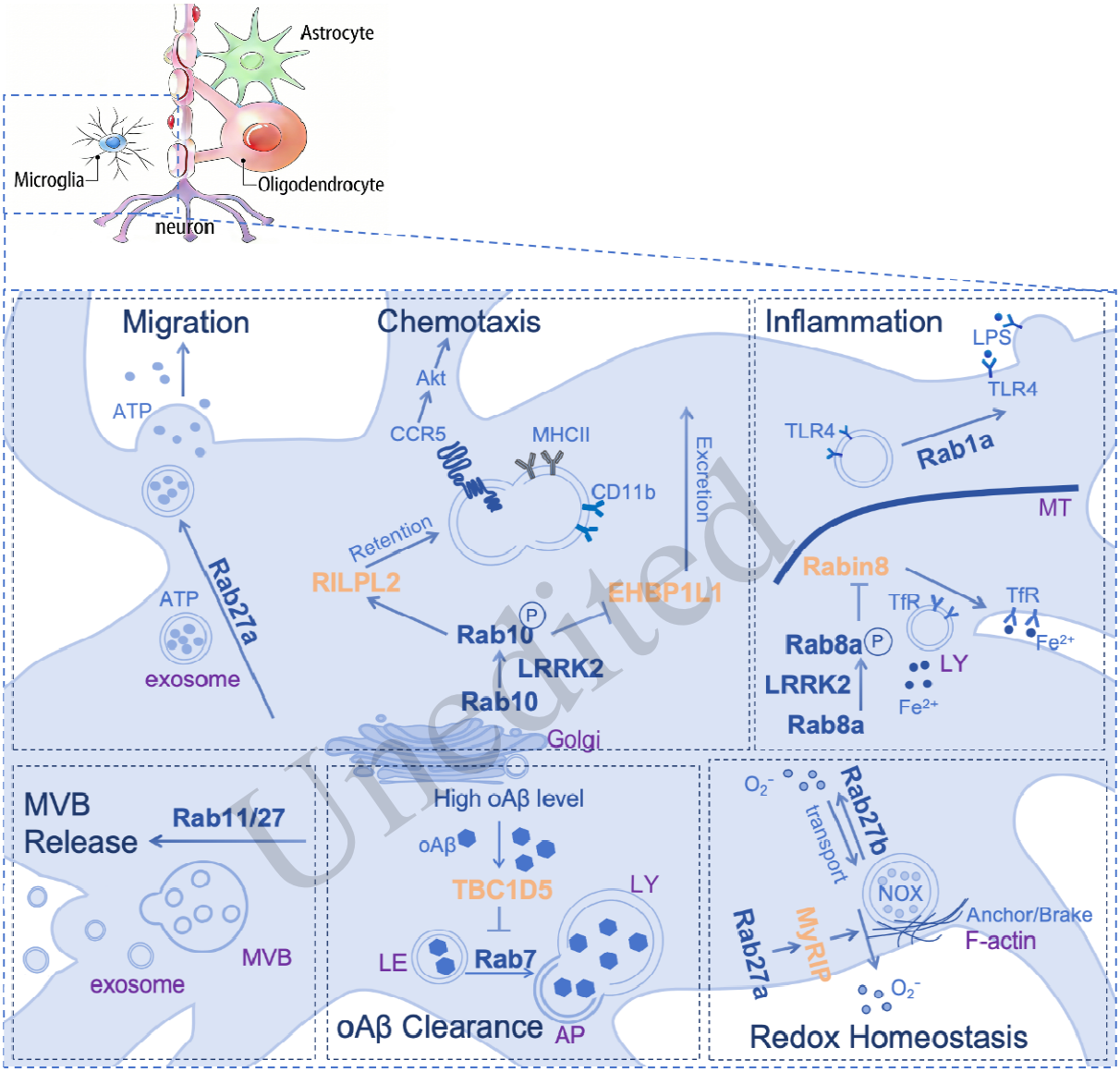

Fig. 1 Overview of Rab GTPase functions in microglia. This schematic summarizes the key roles of Rab GTPases in regulating microglial activities. Rab1a potentiates inflammatory response by promoting TLR4 delivery to the plasma membrane. Rab8a regulates receptor recycling; its aberrant phosphorylation contributes to iron accumulation and neurotoxicity. Rab27a supports ATP-dependent chemotactic migration. Rab10 and its phosphorylated form enhance chemotaxis and phagocytosis via an endosomal signaling platform. Rab11 and Rab27 coordinately regulate exosome secretion, thereby shaping intercellular communication. Rab7 contributes to Aβ clearance, and its dysregulation impairs autophagosome–lysosome fusion. Finally, Rab27a and Rab27b fine-tune reactive oxygen species (ROS) production and inflammation by exerting opposing effects on NADPH oxidase localization. Abbreviations: Early Endosome (EE), Late Endosome (LE), Multivesicular Body (MVB), Lysosome (LY), Autophagosome (AP), Microtubule (MT), Filamentous Actin (F-actin).

3 Function of Rab GTPases in astrocytes

Astrocytes are the most abundant glial cells in the CNS, characterized by numerous fine processes that extend from the soma to form intimate contacts with both cerebral blood vessels and neuronal synapses. Through

these extensive interactions, astrocytes play an indispensable role in maintaining neurotransmitter homeostasis, promoting synapse formation and maturation, and preserving the integrity of the blood-brain barrier (BBB) (Verkhratsky and Nedergaard 2018; Drukarch et al. 1998; Diniz et al. 2012). Increasing evidence indicates that astrocytic dysfunction—often accompanied by altered expression or activity of Rab family proteins—is closely associated with the pathogenesis of several neurodegenerative disorders. Accordingly, this section focuses on summarizing current knowledge regarding the functions and regulatory mechanisms of Rab proteins in astrocytes.

3.1 Rab GTPases coordinate receptor recycling to maintain astrocytic homeostasis

Rab11 orchestrates the recycling of membrane proteins from endosome to the plasma membrane, a process facilitated by its effector proteins, the Rab11 family-interacting proteins (FIPs), which link recycling endosome to motor proteins (Welz et al., 2014; Sultana and Novotny, 2022). In astrocytes, this pathway maintains synaptic homeostasis by controlling the surface expression of key transporters. Zhang et al. demonstrated that Rab11 mediates plasma-membrane delivery of the γ-aminobutyric acid (GABA) transporter (GAT), and its dysfunction impairs synaptic GABA clearance and neuronal activity (Zhang et al., 2017a). Furthermore, Rab11 is responsible for trafficking the TWIK-tandem of pore domains in a weak inward rectifying K+ channel (TWIK-1) to the membrane, a step essential for metabotropic glutamate receptor 3 (mGluR3)-enhancing ammonium uptake. Ammonium is a critical substrate for the glutamate-glutamine cycle. Inhibition of Rab11 membrane anchoring abolishes this process, highlighting the Rab11's role as a functional core for transporter trafficking and as a potential target for modulating neurotransmission in neurodegenerative contexts (Wang et al., 2016). In addition, the endocytic trafficking of aquaporin-4 (AQP4) is coordinately regulated by Rab5 and Rab11. Rab5 mediates the internalization of AQP4 from the plasma membrane, whereas Rab11 facilitates its return via the recycling endosomal pathway. This coordinated transport is microtubule-dependent, as evidenced by its disruption upon treatment with nocodazole. Consequently, dysfunction of either Rab GTPase impairs astrocytic capacity to dynamically regulate water density, potentially leading to a homeostatic imbalance that adversely affects neural function under pathological stress (Markou et al., 2024).

Rab8a is critical for maintaining astrocytic responsiveness by facilitating the surface delivery of key proteins, such as excitatory amino acid transporter 2 (EAAT2), via recycling endosomes. Its inhibition by pathogenic LRRK2-mediated phosphorylation disrupts glutamate-transporter trafficking, leading to excitotoxic neuronal death through calcium-mediated toxicity (Furness et al., 2008; Lau and Tymianski, 2010; Iovino et al., 2022; Bailey and Cookson, 2024). Pharmacological inhibition of LRRK2 kinase activity partially restores EAAT2 membrane localization, indicating that Rab8a phosphorylation represents a disease-relevant and potentially reversible mechanism contributing to excitatory imbalance in PD.

Additionally, the astrocyte-specific Rab31 (formerly known as Rab22b) orchestrates endolysosomal sorting of receptors like epidermal growth factor receptor (EGFR) and mannose-6-phosphate receptor (M6PR), thereby influencing cell development and signaling. While Rab31 dysfunction is implicated in impaired astrocyte reactivity, the mechanisms regulating its activity await elucidation (Ng et al., 2009).

3.2 Rab12 inhibits primary ciliogenesis in astrocytes

A newly discovered astrocytic pathway links Rab12 to the suppression of primary cilia formation, a process independent of its typical functions in lysosomal transport (Xu et al., 2015). Mechanistically, Rab12 forms a critical complex with LRRK2 that enables two key phosphorylation events: first, LRRK2 enhances Rab10 phosphorylation to recruit Rab interacting lysosomal protein like 1 (RILPL1); second, LRRK2 directly phosphorylates Rab12 at Ser106, strengthening its binding to RILPL1/2 (Steger et al., 2017; Lara Ordonez et al., 2019; Li et al., 2024). These effectors then disrupt the membrane trafficking and intraflagellar transport (IFT) necessary for proper ciliary assembly. This pathway, aberrantly active in LRRK2 G2019S models, results in astrocyte ciliary loss, connecting Rab12 dysregulation to the ciliopathies observed in neurological disease (Steger, et al., 2017; Bear et al., 2025). The significance of this mechanism has been validated in both primary astrocytic cultures (in vitro) and the brains of LRRK2 G2019S transgenic mice (in vivo). These findings underscore its critical contribution to the progressive pathogenesis of PD.

3.3 Rab7 in reactive astrogliosis and glial scar formation

The late endosomal GTPase Rab7 has been identified as a pathogenic driver in astrocyte-mediated neuroinflammation following ischemic stroke. It promotes reactive proliferation and glial scar formation. Targeting this pathway, Qin et al. demonstrated the therapeutic efficacy of CID1067700, a specific Rab7 antagonist. The compound suppresses Rab7 activity, potentially by disrupting syntaxin 11-mediated endosome–lysosome fusion. This intervention curbs the pathological cytosolic leakage of cathepsin B, a key event in inflammation-induced cell death. These studies, which utilized the transient middle cerebral artery occlusion (tMCAO) rat model and OGD/R-treated primary astrocytes, provide robust evidence at both the cellular and organismal levels for the therapeutic potential of Rab7 antagonism. These findings demonstrate that targeting Rab7 can effectively mitigate the damage associated with ischemic injury. Consequently, treatment with CID1067700 attenuates brain atrophy, inhibits reactive astrogliosis, and significantly improves functional neurological recovery (Qin et al., 2019).

3.4 Rab GTPases as orchestrators of HIV-1 endocytic entry in astrocytes

The endocytosis-mediated entry of human immunodeficiency virus type 1 (HIV-1) into astrocytes is a key factor behind the virus's elusive behavior in these cells. This intricate process is governed by the coordinated actions of Rab5, Rab7, and Rab11, which orchestrate the virus's journey through the endocytic pathway. Studies demonstrate that knockout of this Rab triad disrupts the entire transport cascade, effectively blocking HIV-1 infection by impairing viral endocytic efficiency and infectivity. This protective strategy safeguards astrocytes and neurons from damage, underscoring the critical role of Rab-mediated trafficking in viral persistence (Chauhan et al., 2014; Chauhan and Khandkar, 2015). These conclusions were primarily derived from in vitro studies using cultured primary human fetal astrocytes (HFA), highlighting the role of Rab-dependent endocytic trafficking in HIV-1 infection. This finding will facilitate future efforts to elucidate the contribution of low-level infections to neurological complications.

3.5 Rab35 regulates MTMR to repress astrocyte hypertrophy

Rab35 plays a critical role in repressing mammalian target of rapamycin complex 1 (mTORC1) signaling to control astrocytic growth by regulating phosphoinositide turnover. Sawade et al. demonstrated that in astrocytes, Rab35 forms a functional complex with the lipid phosphatases myotubularin-related protein 2 (MTMR2) and MTMR13. The loss of Rab35 disrupts this complex, leading to a pathological accumulation of phosphoinositides Phosphatidylinositol 3-Phosphate (PI(3)P) and Phosphatidylinositol 3,5-Bisphosphate ($PI(3,5)P_2$). This elevated phosphoinositide level, in turn, hyperactivates mTORC1—a key regulator of cell growth. Aberrant activation of mTORC1 drives astrocyte hypertrophy (Sawade et al., 2020).

3.6 Rab GTPases orchestrate directed vesicle trafficking in astrocytes for neuronal support

Rab GTPases coordinate distinct facets of vesicular trafficking in astrocytes. Rab4 and Rab5 regulate the cytoskeletal coupling that determines directional vesicle motility; disruptive mutants confirm that impaired GTPase cycling reduces directional movement, potentially disrupting critical astrocyte-neuron communication (Potokar et al., 2007; Potokar et al., 2012). In parallel, Rab6a identifies a separate vesicular population originating from the trans-Golgi network (TGN). Its localization to peripheral processes suggests a role in the distal exocytosis of signaling molecules, positioning Rab6a+ vesicles as key mediators of astrocytic influence on synaptic activity and implicating their dysfunction in neurodegenerative pathways (Melzer et al., 2021).

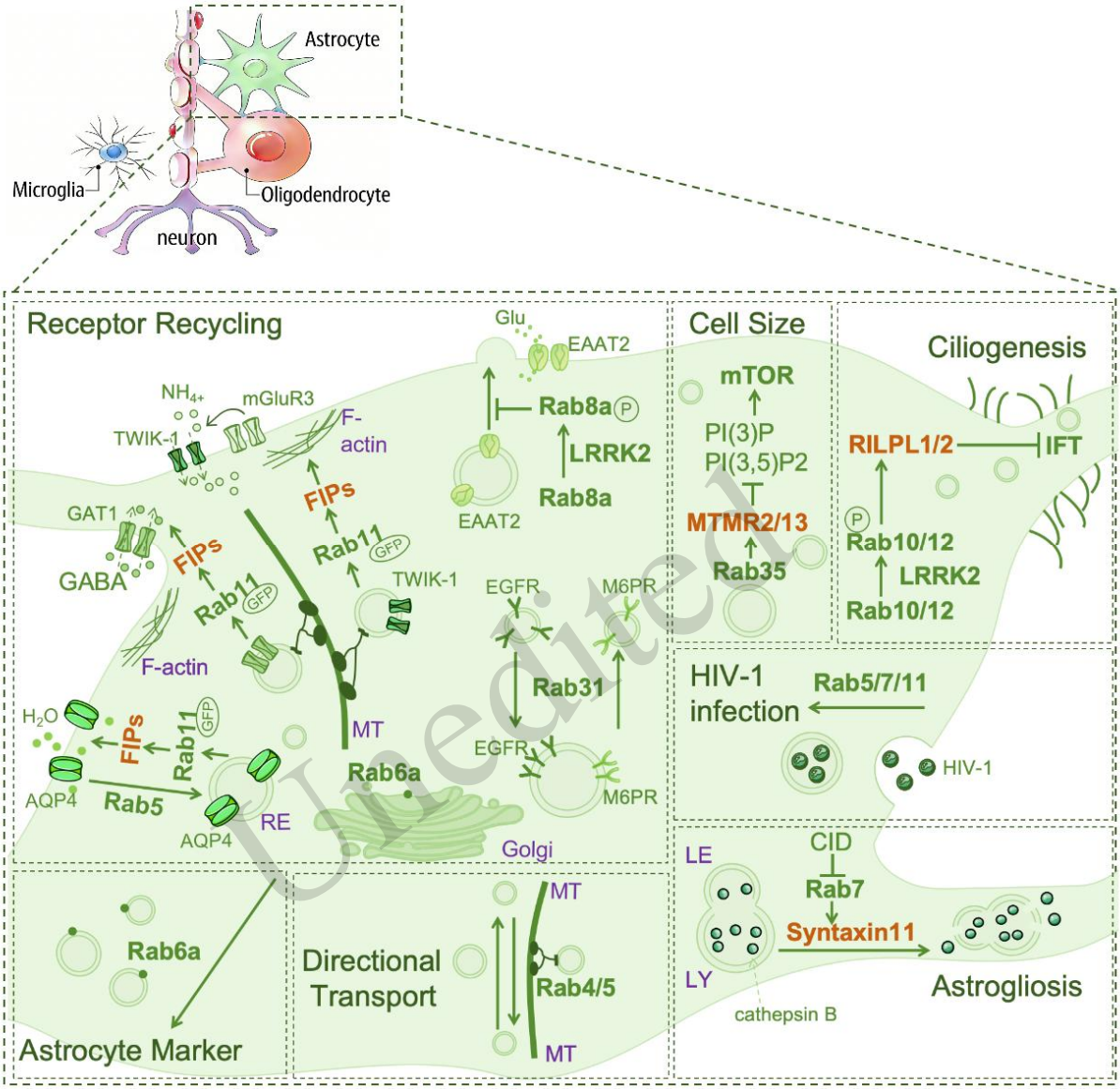

Fig. 2. Overview of Rab GTPase functions in astrocytes. The schematic highlights key Rab-dependent pathways. Rab5 and Rab11 coordinately regulate endocytosis and recycling in the water channel AQP4. Rab8A mediates plasma-membrane trafficking of EAAT2 to maintain glutamate homeostasis. Rab12 cooperates with LRRK2 to suppress primary ciliogenesis. Rab7 drives reactive astrogliosis and glial scar formation. Rab5, Rab7, and Rab11 collectively govern the endocytic entry pathway of HIV-1. Rab35 represses mTORC1 signaling via the MTMR complex to restrain cellular hypertrophy. Rab4 and Rab5 regulate directional vesicle motility. Rab6a marks TGN-derived vesicles destined for distal exocytosis of signaling molecules. Abbreviations: Recycling Endosome (RE), Late Endosome (LE), Lysosome (LY), Microtubule (MT), Filamentous Actin (F-actin).

4 Function of Rab GTPases in oligodendrocytes

Oligodendrocyte precursor cells (OPCs) differentiate into mature oligodendrocytes that generate myelin sheaths, providing electrical insulation for axons and enabling rapid saltatory conduction (Miyamoto et al., 2014). To sustain the synthesis and long-term maintenance of extensive myelin membranes, oligodendrocytes rely heavily on highly coordinated vesicular trafficking pathways. These trafficking processes regulate targeted delivery of lipids, membrane proteins, and myelin components to specialized membrane domains

(Huber et al., 1994). Rab GTPases, as key molecular switches of the endomembrane system, are key in orchestrating this transport—controlling vesicle budding, motility, and fusion events critical for myelin biogenesis. Dysregulation of Rab-dependent trafficking or myelin turnover has been increasingly implicated in disruption of oligodendrogenesis and myelin integrity, contributing to the onset and progression of neurodegenerative diseases such as MS and AD (Braak and Braak, 1996).

4.1 Rab GTPases orchestrate vesicular trafficking in oligodendroglial myelination

Myelination by oligodendrocytes depends on finely tuned vesicular transport and membrane fusion to ensure correct delivery of lipids and myelin proteins. Several Rab GTPases act as key molecular regulators of these processes. Rab3a localizes to vesicular compartments that partially overlap with early endosome and promotes morphological maturation and myelin formation by increasing biosynthesis of proteolipid protein (PLP) and directing PLP to the plasma membrane (Anitei et al., 2009). Through GTP-dependent binding to synaptosomal-associated protein 29 (SNAP-29), Rab3a mediates vesicle membrane fusion, while its GDP dissociation inhibitor (GDI) contributes to proper vesicle turnover (Motoike et al., 1993; Schardt et al., 2009). Rab10, together with myristoylated alanine-rich C-kinase substrate (MARCKS) and myosin Vb (MYO5B), regulates trafficking and membrane insertion of Rab10-positive precursor vesicles carrying myelin basic protein (MBP) and other myelin constituents (Liu et al., 2013; Xu et al., 2014; Zhang et al., 2017c). Disrupting the Rab10-MARCKS interaction impairs vesicle docking and membrane expansion, which reduces oligodendrocyte maturation (Zhang et al., 2017b). Rab27b supports lysosome-mediated secretion of PLP; its depletion hinders lysosome proximity to the plasma membrane and decreases myelin-like membrane formation in neuron-oligodendrocyte co-cultures (Shen et al., 2016).

Rab31 plays a multifaceted role in orchestrating myelin protein trafficking from the TGN in oligodendrocytes. Specifically, Rab31 mediates TGN-to-endosome transport of myelin components in a GTP-dependent manner (Burcelin et al., 1997; Rodriguez-Gabin et al., 2001; Larocca and Rodriguez-Gabin, 2002) and recruits the inositol 5-phosphatase oculo-cerebro-renal syndrome of lowe protein 1 (OCRL-1) to the TGN, thereby supporting M6PR transport and maintaining myelin structural integrity (Rodriguez-Gabin et al., 2009; Rodriguez-Gabin et al., 2010).

Together, these findings establish Rab GTPases as essential coordinators of vesicular trafficking in oligodendrocytes, integrating endosomal transport, secretion, and membrane remodeling to sustain myelin formation and white-matter integrity.

4.2 Rab11 regulates oligodendrocyte morphogenesis

Rab11a, a key regulator of endosomal recycling to the plasma membrane, controls the membrane supply necessary for oligodendrocyte morphogenesis. While the active Rab11a-Q70L mutant generally enhances protrusion branching and coverage, a disease-associated mutant, Rab11a-R33P, reveals a more complex phenotype. It causes an imbalance (excessive branching coupled with thinner processes and restricted coverage) which is detrimental to myelination. Mechanistically, R33 residue is critical for interacting with cytoskeletal transport mediators like Myosin V and FIP3. The R33P mutation likely abrogates these interactions, leading to aberrant vesicle delivery and the observed morphological deficits that ultimately disrupt myelin assembly (Tsuneura et al., 2023).

4.3 Rab9 and Rab40c in oligodendrocyte differentiation

The transition of oligodendrocytes from precursors to myelinating cells requires a precise shift in vesicular trafficking, governed by different Rab GTPases. Rab9 predominantly localizes to the TGN and late endosome, where it mediates bidirectional trafficking between these compartments and lysosomes (Lombardi et al., 1993). Beyond its canonical role in late endosomal transport, emerging evidence indicates that Rab9 participates in autophagosome–lysosome fusion (Kucera et al., 2016). Recent work by Fukushima et al. revealed that Rab9 knockdown in oligodendrocytes promotes extensive membrane outgrowth and enhances expression of myelin proteins such as PLP and MBP, resulting in a more differentiated cellular phenotype (Fukushima et al., 2024). Using the FBD-102b oligodendrocyte precursor cell model, these findings suggest that Rab9 normally acts as a negative regulator of oligodendrocyte morphological differentiation, likely by facilitating autophagic degradation of myelin-associated components. When Rab9 activity is reduced, impaired

autophagosome–lysosome fusion may attenuate myelin protein turnover, thereby favoring myelin accumulation and process extension. These results reveal a specialized role for Rab9 in oligodendroglial cell morphological changes, suggesting its potential as a therapeutic target for mitigating diseases such as hypomyelinating leukodystrophy type 1 (HLD1).

Rab40c, in contrast, localizes primarily to the perinuclear recycling compartment (PRC) and to vesicular and tubular structures adjacent to the Golgi apparatus. Interestingly, Rab40c expression is markedly elevated in mature oligodendrocytes but remains low in OPCs, pointing to a role in the vesicular trafficking of myelin components during later stages of differentiation (Rodriguez-Gabin et al., 2004).

4.4 Rab27a-dependent vesicular trafficking facilitates HSV-1 infection in oligodendrocytes

Viral infections have been implicated as potential triggers of demyelinating disorders, including MS (Noseworthy, 1999). A previous study identified Rab27a as an important regulator of herpes simplex virus type 1 (HSV-1) infection in oligodendrocytes. Rab27a predominantly colocalizes with HSV-1 envelope proteins in the TGN, suggesting its involvement in the late stages of viral assembly and trafficking. Functional analyses reveal that Rab27a knockdown does not impair viral entry but markedly reduces viral infectivity, leading to fewer and smaller plaques as well as significantly decreased viral yield (Bello-Morales et al., 2012)(Bello-Morales et al. 2012). These findings indicate that Rab27a facilitates the packaging and transport of nascent viral particles from the TGN to the plasma membrane, thereby promoting efficient viral replication and egress. Given the established association between viral infection and demyelination, Rab27a-mediated vesicular trafficking may represent a mechanistic link between oligodendrocyte infection and pathogenesis of demyelinating diseases.

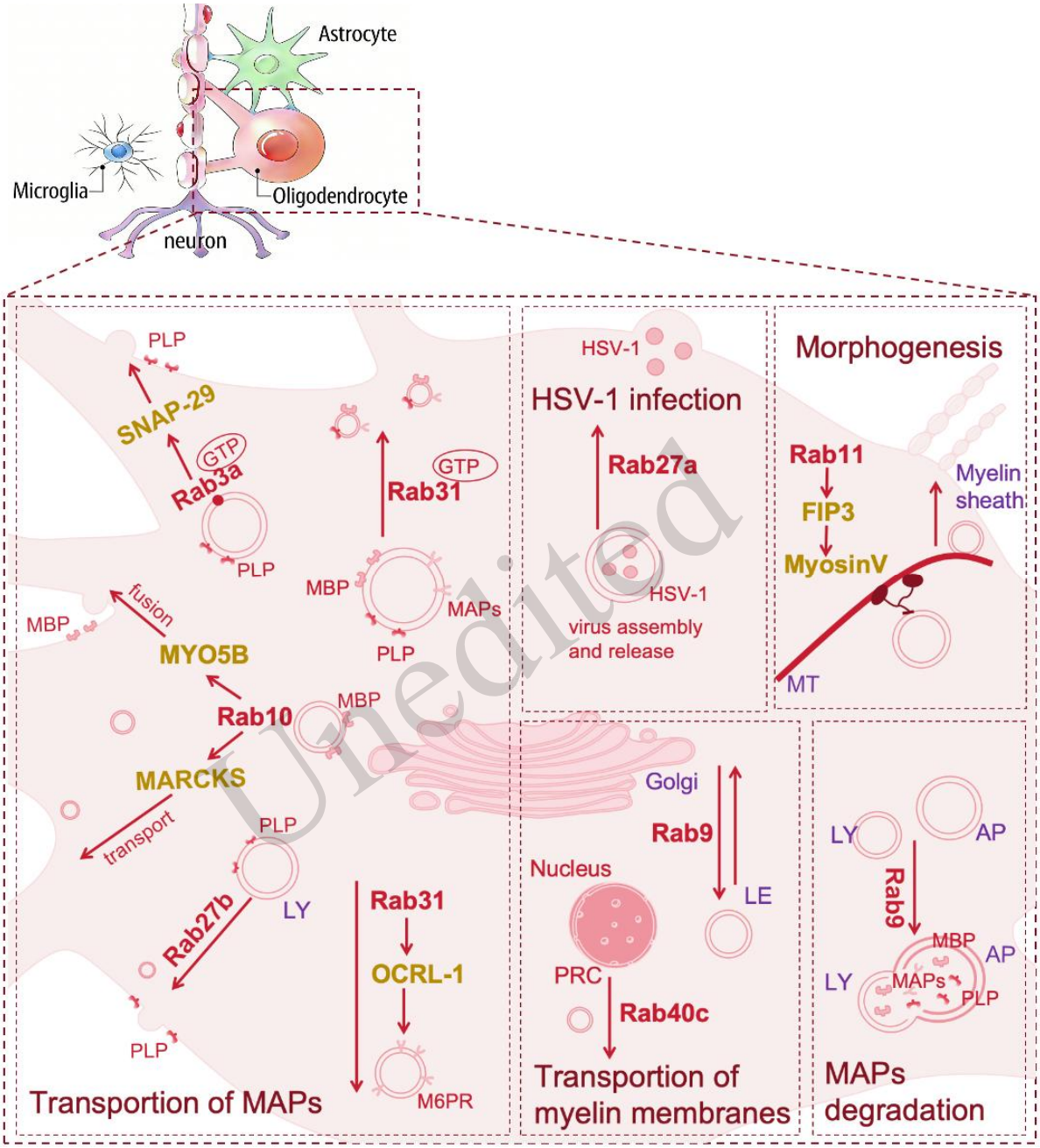

Fig. 3. Overview of Rab GTPase functions in oligodendrocytes. This schematic summarizes representative Rab-regulated pathways in oligodendrocytes. Rab3a promotes PLP synthesis and plasma-membrane targeting, while Rab27b facilitates lysosome-dependent secretion of PLP. Rab10 cooperates with MARCKS and MYO5B to transport myelin components such as MBP. Rab31 regulates trafficking from the TGN to endosomes. Rab11a contributes membrane supply for morphogenesis; the Rab11a R33P mutant causes morphological deficits. Rab9 negatively regulates differentiation and has been implicated in autophagosome-lysosome fusion. Rab40c is highly expressed in mature oligodendrocytes to support trafficking of myelin components. Rab27a promotes HSV-1 assembly and egress, linking viral trafficking to demyelinating diseases. Abbreviations: Late Endosome (LE), Lysosome (LY), Autophagosome (AP), Microtubule (MT).

5 Convergent roles of Rab GTPases in neurodegenerative pathologies

Rab GTPases exhibit convergent roles across glial cell types in the pathogenesis of specific neurodegenerative diseases, including AD, PD, and MS, by dysregulating vesicular trafficking, inflammatory signaling, and cellular homeostasis. In AD, oAβ in microglia impairs the Rab5-to-Rab7 transition during endosomal maturation, leading to lysosomal membrane damage, reduced Aβ clearance, and a vicious cycle of neurodegeneration exacerbated by upregulated TBC1D15-mediated Rab7 inactivation (Yao, et al., 2019; Wu, et al., 2024). Rab10 has been identified as a positive regulator of microglial phagocytosis (Liu, et al., 2020), a process fundamental to Aβ clearance. Consequently, its dysfunction may represent a distinct layer of vesicular trafficking impairment that contributes to the pathological cascade of AD. In PD, LRRK2-mediated phosphorylation of Rab8a in microglia and astrocytes disrupts receptor recycling (e.g., TfR and EAAT2), promoting iron accumulation, neuroinflammation, and excitatory imbalance (Mamais, et al., 2021; Bailey and Cookson, 2024). Similarly, Rab12 and Rab10 in astrocytes, hyperphosphorylated by LRRK2 G2019S, inhibit primary ciliogenesis via RILPL1/2 recruitment and PIP_2 dysregulation, leading to ciliary loss and progressive PD pathology (Steger, et al., 2017; Bear, et al., 2025). For MS, oligodendroglial Rab GTPases like Rab35, Rab27b, and Rab9 regulate myelin protein trafficking (e.g., PLP and MBP) and differentiation; their dysregulation contributes to demyelination and hypomyelinating disorders like HLD1 (Miyamoto, et al., 2014; Fukushima, et al., 2024). Additionally, Rab27a facilitates HSV-1 trafficking in oligodendrocytes, potentially triggering MS-like demyelination (Bello-Morales, et al., 2012). Collectively, these Rab-mediated disruptions underscore shared glial vulnerabilities in AD, PD, and MS, positioning Rab GTPases as promising therapeutic targets for modulating glial-neuronal interactions and disease progression.

6 Discussion

Rab GTPases have emerged as master regulators of vesicular trafficking across all glial cell types, integrating intracellular transport, membrane remodeling, and signaling to maintain CNS homeostasis. In microglia, Rab GTPases orchestrate receptor recycling, chemotactic migration, and exosome-mediated communication; in astrocytes, they regulate endocytic and exocytic trafficking to sustain neurotransmitter clearance, blood–brain barrier integrity, and lipid metabolism; and in oligodendrocytes, they direct the delivery of lipids and myelin proteins essential for axonal insulation. Together, these findings position Rab GTPases as critical molecular switches that coordinate glial functions with remarkable spatial and temporal precision.

6.1 Cell-type-specific Rab function in glia

Different glial populations contribute to neurodegenerative disease through distinct pathological mechanisms, including neuroinflammation, synaptic dysregulation, and demyelination. Therefore, recognizing the cell-type-specific functions of Rab GTPases is essential for understanding how Rab dysregulation influences disease progression in a glial-subtype–dependent manner. The functional specificity of Rab proteins arises from differences in their expression profiles and organelle organization, as well as the specialized physiological roles of individual glial cell types. For instance, Rab5- and Rab7-dependent endosomal maturation is particularly prominent in microglia, which possess abundant phagolysosomes and highly dynamic endosomal systems. Consequently, these Rabs play critical roles in pathogen clearance, synaptic pruning, and inflammatory signaling in microglia. In contrast, Rab4-, Rab8-, and Rab11-mediated trafficking pathways that regulate exocytosis, recycling endosomes, and membrane turnover are especially important in astrocytes, supporting gliotransmitter release and receptor recycling. Meanwhile, Rab6- and Rab27-associated polarized trafficking is required in oligodendrocytes to ensure the efficient delivery of myelin components to expanding myelin sheaths. Elucidating this cell-type specificity of Rab proteins is not only important for advancing our fundamental understanding of glial biology but may also reveal glia-selective therapeutic targets for neurodegenerative diseases while minimizing off-target effects. Moreover, current knowledge largely derives from a subset of "classical" Rab GTPases; the vast landscape of “non-classical” Rab proteins remains largely unexplored in the context of microglia, astrocytes, and oligodendrocytes. While this review

focuses on Rabs with established glial functions, it is important to acknowledge members like Rab21, whose crucial roles in neuronal endocytosis, APP processing, and migration suggest they may also exert significant, yet currently under-studied, influence on glial homeostasis (Sun et al., 2018; Peralta Cuasolo et al., 2023; Shikanai et al., 2023). This knowledge gap constitutes a promising avenue for future investigation.

Moreover, glial Rab GTPases are often studied in isolation, without consideration of the broader Rab network or the effector cascades that confer specificity on their actions. This reductionist approach limits our understanding of how Rab-regulated pathways are hierarchically organized and dynamically coordinated within the highly polarized architecture of glial cells.

A major challenge for future research lies in elucidating the cell-type- and context-specific mechanisms that determine Rab GTPase function. The same Rab proteins can exert divergent or even opposing effects depending on the cellular environment. For example, Rab10 enhances endosomal signaling and chemotaxis in microglia but mediates pathological vesicle trafficking and α-synuclein aggregation in neurons. Similarly, Rab35 plays a dual role in oligodendrocytes: it restricts myelination by inhibiting Arf6 via the ACAP2-dependent pathway (Donaldson and Jackson, 2011; Yamauchi et al., 2012; Miyamoto, et al., 2014). In contrast, at the plasma membrane, Rab35 can facilitate vesicle docking and exosome secretion, thereby promoting PLP release (Hsu et al., 2010). Collectively, such discrepancies highlight the need to define the local regulatory milieu—proximal regulators, cytoskeletal organization, and effector availability—that shapes Rab activity in each glial subtype (Kiral et al., 2018; Mignogna and D'adamo, 2018). Moreover, post-translational modifications such as phosphorylation by LRRK2, prenylation, and ubiquitination dynamically modulate Rab localization and activity (Shinde and Maddika, 2018). Understanding how these modifications integrate environmental cues such as inflammation, oxidative stress, or metabolic state into Rab-dependent trafficking decisions will be crucial for determining glial plasticity under physiological and disease conditions.

6.2 Implications for clinic translation

Another key frontier is the translation of basic Rab biology into therapeutic innovation. However, efforts to modulate Rab activity pharmacologically are still in their infancy (Jordan et al., 2022). Rab GTPases have traditionally been viewed as "undruggable" due to their high affinity for GTP/GDP and lack of accessible allosteric pockets. Nevertheless, recent progress in structure-based drug design, fragment screening, and covalent ligand chemistry has begun to challenge this assumption. Encouragingly, the successful development of small-molecule inhibitors which target oncogenic Ras variants—such as KRAS G12C inhibitors—demonstrates that selective covalent targeting of GTPases is feasible (Janes et al., 2018; Skoulidis et al., 2021). These compounds exploit unique conformational vulnerabilities and nucleotide-cycling intermediates, offering a blueprint for designing Rab-specific modulators (Ostrem et al., 2013). Adapting these principles to the Rab subfamily could yield novel pharmacological tools to restore vesicular homeostasis in glial cells.

Beyond covalent inhibition, proteolysis targeting chimera (PROTAC) technology offers another strategy to tackle the 'undruggable' nature of Rab GTPases. Drawing inspiration from the recent clinical breakthrough of KRAS G12C degraders, which leverage heterobifunctional molecules to recruit E3 ubiquitin ligases (e.g., von hippel-lindau (VHL) or Cereblon) for targeted proteasomal degradation (Bond et al., 2020), a similar approach could be tailored for the Rab subfamily. Unlike traditional inhibitors that require high-affinity binding to active sites, Rab-targeted PROTACs may achieve potent silencing by exploiting even transient surface-binding pockets (Sun et al., 2019; Burslem and Crews, 2020).

In addition to directly targeting Rab proteins, alternative therapeutic strategies may involve modulating components of the Rab regulatory network, including Rab GEFs, GAPs and downstream effectors that control vesicular trafficking dynamics. The clinical advancement of LRRK2 inhibitors (e.g., BIIB122) targeting the Rab8/10 phosphorylation axis represents a landmark in Rab-related drug discovery for PD (Jennings et al., 2023). Beyond direct enzymatic inhibition, the focus is shifting toward modulating the Rab interactome and specifically targeting GEFs or GAPs to restore homeostatic flux in glia. Such approaches may provide greater specificity and pharmacological tractability than targeting Rab proteins themselves.

Increasing evidence suggests that glial cells represent promising therapeutic entry points for restoring vesicular homeostasis in neurodegenerative disease. However, several challenges remain for clinical translation, including achieving cell-type–specific targeting within the central nervous system, overcoming

blood–brain-barrier constraints, and minimizing systemic effects on ubiquitous trafficking pathways.

7 Perspectives

Technological advances now provide powerful opportunities to address these questions. Super-resolution live imaging and cryo-electron tomography can visualize Rab-driven vesicle dynamics in three dimensions at nanometer resolution. Integration of single-cell RNA sequencing with spatial transcriptomics enables mapping of cell-type–specific Rab gene-expression patterns across glial subtypes during disease progression. However, it is important to emphasize that Rab transcript abundance does not necessarily reflect Rab functional activity, as the functional roles of Rab proteins primarily depend on their activation state (GTP/GDP loading), subcellular localization, and post-translational modifications. These findings can be functionally validated using patient-specific induced pluripotent stem cell (iPSC)-derived glial models (e.g., iMicroglia, iAstrocytes), which recapitulate key aspects of human disease pathology. Meanwhile, conditional knockout and knock-in mouse models—particularly those employing cell-type–specific Cre lines—will be indispensable for validating the in vivo relevance of Rab-mediated trafficking to glial physiology, myelination, and neuroinflammation. Integrating these datasets with computational network modeling may ultimately reveal higher-order Rab regulatory modules that govern organelle communication and cellular adaptation in glia.
Ultimately, a convergence of mechanistic insight and translational innovation will determine the future trajectory of this field. Rab GTPases occupy a pivotal nexus between membrane trafficking, cytoskeletal dynamics, and signaling—core cellular processes that are profoundly dysregulated across neurodegenerative diseases. A systematic investigation of their glial functions will therefore not only advance our fundamental understanding of CNS homeostasis but also reveal novel therapeutic avenues to rebalance vesicular dynamics, thereby preserving neuronal and glial integrity.

Search strategy and selection criteria

This review was conducted using a structured literature-search strategy. We retrieved publications from PubMed databases up to [September, 2025] using combinations of the following keywords: “Rab & glia”, “Rab & microglia”, “Rab & astrocyte”, “Rab & oligodendrocyte”, and “Rab & Neurodegeneration” (as well as specific disorders such as “Rab & Alzheimer’s disease”, “Rab & Parkinson’s disease”, and “Rab & Multiple Sclerosis”). Studies were prioritized for inclusion based on the following criteria: (i) primary research providing direct experimental evidence of a Rab-mediated pathway in at least one of the three major CNS glial types; (ii) studies offering mechanistic insights into how Rab dysregulation drives neurodegenerative pathology; and (iii) landmark papers or high-impact recent publications that have significantly shaped the current understanding of the field. To minimize citation bias, both confirmatory and contradictory findings were considered. Articles were excluded if they lacked clear mechanistic focus or if the Rab-related findings were solely based on non-CNS cell lines without subsequent validation in glial models.

Data availability statement

The content of this article is all derived from published articles. It can be accessed and downloaded through public websites.

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Author contributions

Ruofan ZHOU: conceptualization, writing – original draft, and visualization. Fulong LI: funding acquisition and writing – review & editing. All authors have read and approved the final version.

Compliance with ethics guidelines

Ruofan ZHOU, and Fulong LI declare that they have no conflicts of interest.
This review does not contain any studies with human or animal subjects performed by any of the authors.

Declaration on the use of generative AI tools

During the preparation of this work, Ruofan ZHOU used deepseek in order to improve language and readability, check for grammatical errors. After using this tool, Ruofan ZHOU reviewed and edited the content as needed and take full responsibility for the content of the publication.

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