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Review Article

Insights into the cellular consequences of LRRK2-mediated Rab protein phosphorylation

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Point mutations in leucine-rich repeat kinase 2 (LRRK2) which cause Parkinson's disease increase its kinase activity, and a subset of Rab GTPases have been identified as endogenous LRRK2 kinase substrates. Their phosphorylation correlates with a loss-of-function for the membrane trafficking steps they are normally involved in, but it also allows them to bind to a novel set of effector proteins with dominant cellular consequences. In this brief review, we will summarize novel findings related to the LRRK2-mediated phosphorylation of Rab GTPases and its various cellular consequences *in vitro* and in the intact brain, and we will highlight major outstanding questions in the field.

Introduction

Parkinson's disease (PD) is a progressive, debilitating neurodegenerative disorder without a cure. The motor symptoms include tremor, rigidity and slowness of movement, and are due to the degeneration of dopaminergic neurons in the substantia nigra pars compacta. PD currently affects an estimated 7 million people and is the fastest-growing neurodegenerative disorder worldwide [1]. It is largely a sporadic disease of unknown etiology, with age being the biggest risk factor. However, ~10% of PD cases are due to autosomal-dominant or autosomal-recessive mutations in certain genes, and this allows for disease modeling in cellular systems and in animal models to understand the underlying mechanism(s).

Point mutations in the gene encoding for leucine-rich repeat kinase 2 (LRRK2) are the most common cause of familial PD and are inherited in an autosomal-dominant fashion [2–5]. PD due to mutations in LRRK2 causes late-onset disease clinically largely indistinguishable from sporadic PD, even though LRRK2-PD patients present with pleomorphic pathology which is distinct from that observed in sporadic PD [6]. In addition, sequence variations in LRRK2 have been described to positively or negatively modify disease risk [7,8]. Thus, LRRK2 seems to play an important role in the entire PD spectrum, and due to its druggable nature has become the focus of significant research efforts.

LRRK2 domain structure and kinase substrates

LRRK2 is a large multi-domain enzyme which belongs to the ROCO type protein family, characterized by a ROC (Ras of complex) GTPase domain followed by a COR (C-terminal of ROC) and a kinase domain [9]. Apart from such catalytic core, additional protein interaction domains are present including armadillo, ankyrin and leucine-rich repeat domains at the N-terminus, and a WD40 repeat domain at the C-terminus of LRRK2. Seven pathogenic mutations have been described which are located in the ROC domain (N1437H, R1441C/G/H), COR domain (Y1699C) and kinase domain (G2019S, I2020T), respectively.

LRRK2 is highly expressed in the lung, kidney, intestine and various immune cells, with significantly lower levels detected in the brain [10,11]. Phosphoproteomics analysis in MEFs (murine embryonic fibroblasts) and in immune-stimulated PBMCs (peripheral blood mononuclear cells) identified a small subset of Rab GTPases, key regulators of membrane trafficking steps as endogenous LRRK2 kinase substrates [12,13]. Rab10 was identified as the top hit in both cases, but additional Rab proteins, including Rab3, Rab8, Rab12, Rab35 and Rab43, were subsequently shown to be phosphorylated

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by endogenous LRRK2 [14]. Rab1 is not an endogenous substrate for pathogenic LRRK2 [14]. However, a point mutant in vps35 which causes autosomal-dominant PD (vps35-D620N) causes increased Rab1 phosphorylation in a manner mitigated by LRRK2 kinase inhibitors [11], suggesting that certain LRRK2 activators may redirect the Rab substrate specificity of LRRK2 by unknown means. Whilst the Rabs are the only independently validated endogenous LRRK2 substrates known to date, additional and perhaps tissue-specific, cell type-specific and context-dependent LRRK2 kinase substrates may exist as well.

In MEF cells, Rab10 is the preferred substrate for LRRK2 followed by Rab8 and Rab35, a preference which is mirrored by the relative abundance of these Rab proteins [11]. In mouse tissues, there are differences in phosphorylation preference, with Rab10 being the most prominent LRRK2 substrate in the lung, but not in spleen or kidney [11]. In brain extracts, Rab10 phosphorylation levels are hardly detectable [10,11,15], but Rab12 phosphorylation is prominently regulated by endogenous pathogenic LRRK2 or by LRRK2 kinase inhibitors [16]. The phosphatase PPM1H is known to dephosphorylate Rab8, Rab10 and Rab35, but has little effect on the phosphorylation levels of Rab12 [17]. Since PPM1H is highly expressed in brain as compared with other tissues [17], its presence may explain the difficulty in detecting brain-derived steady-state levels of phospho-Rab10 as compared with phospho-Rab12. Altogether, current data suggest that the relative abundance of Rab proteins combined with the specificity/abundance of the Rab phosphatase(s) may result in distinct combinations of phosphorylated Rab proteins in a tissue-specific and perhaps even cell type-specific manner.

All currently described pathogenic mutations increase the LRRK2 kinase activity, albeit by distinct means. Only the G2019S-LRRK2 mutation increases the LRRK2 kinase activity *in vitro* [18–20]. As assessed in cells and tissues, the G2019S-LRRK2 mutation displays increased autophosphorylation at Ser1292 but causes only a modest increase in Rab10 phosphorylation [12,21,22]. In contrast, pathogenic mutations in either the ROC or COR domain display modest effects on Ser1292 autophosphorylation but markedly increase Rab10 phosphorylation [21]. These data suggest that the G2019S-LRRK2 mutation in the activation segment causes an intrinsically more active kinase without altering its subcellular localization. In contrast, R1441C-LRRK2 or Y1699C-LRRK2 may be preferentially localized to the subcellular site(s) proximal to Rab10, and therefore able to cause increased Rab10 phosphorylation in the absence of altered kinase activity *per se* (see also below).

Cellular consequences of LRRK2-mediated Rab phosphorylation

LRRK2 phosphorylation requires the Rab proteins to be membrane-bound and GTP-bound [23,24]. Phosphorylation occurs on a conserved residue in the switch II domain which is critical for the interaction of the Rabs with both regulatory and effector proteins. Consequently, the phosphorylated Rab proteins lose their interaction with the GDP dissociation inhibitor (GDI), which is required to extract them from the membrane [12,14,25]. In addition, and at least as determined for Rab8, the phosphorylated Rab protein also loses its interaction with the GDP/GTP exchange factor (GEF) Rabin8 [12,25] and with certain effectors such as OCRL1 [14,26] but not MICAL-L1 [26,27]. Conversely, phosphorylated Rab10 loses its interaction with the GTPase-activating protein (GAP) TBC1D4/AS160 [23], and overexpression of this GAP protein fails to modulate endogenous levels of phosphorylated Rab8 or Rab10 [28]. This is consistent with structural studies which predict a steric clash mediated by the phospho-residue within the Rab proteins which impairs their interactions with GEF and GAP proteins [12,26]. Therefore, the phosphorylated GTP-bound Rabs will accumulate in their membranous compartments in a manner unable to bring about at least some of the membrane trafficking steps they are normally involved in. Consistent with such predicted loss-of-function type mechanism, we and others have shown that pathogenic LRRK2 impairs Rab8- and Rab10-mediated endocytic recycling and endolysosomal membrane trafficking steps [29–31]. Whilst only a small fraction of total Rabs are phosphorylated by pathogenic LRRK2 under steady-state conditions [32,33], such changes are likely disease-relevant, since entirely blocking Rab8 or Rab10 function has drastic negative consequences for cell and organismal viability [34,35]. Importantly, and in addition to losing their ability to interact with known regulatory and effector proteins, phosphorylation of Rab8 and Rab10 enables them to bind to novel effector proteins including RILPL1, RILPL2, JIP3 and JIP4 [14,26]. These novel phospho-Rab/protein interactions may then cause cellular alterations in a dominant fashion, even though it remains unclear which interactions are the most prominent ones, and under which conditions and in which cell types they occur. In addition, studies are further complicated by the observation that phosphomimetic or nonphosphorylatable Rab mutants do not mimic the phospho- or dephospho-status of the Rab proteins [36].

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RILPL2 expression seems limited to cells of the multiciliated cell lineage, whilst RILPL1 plays a centrosomal/ciliary function in non-multiciliated cells [37]. Therefore, studies have largely focused on the phospho-Rab/RILPL1 interaction. RILPL1 binds with great preference to phospho-Rab8 and phospho-Rab10 [14]. Under normal physiological conditions, RILPL1 localizes to the subdistal appendage of the mother centriole and recruits phospho-Rab8 and phospho-Rab10 to this location [38,39]. The centriolar phospho-Rab/RILPL1 complex formed due to pathogenic LRRK2 kinase activity then causes deficits in ciliogenesis and in the appropriate cohesion between duplicated centrosomes in a plethora of cell types *in vitro* [24,25,28,38,39]. Mechanistically, the centriolar phospho-Rab/RILPL1 complex impairs ciliogenesis by interfering with the recruitment of tau tubulin kinase 2, which is essential for ciliogenesis induction by removing CP110 from the mother centriole [40]. Conversely, in dividing cells the centriolar phospho-Rab/RILPL1 complex causes a centrosomal cohesion deficit by interfering with the recruitment of cdk5rap2, a protein essential for maintaining the duplicated centrosomes in close proximity [28]. Hence, the same centriolar phospho-Rab/RILPL1 complex triggered by pathogenic LRRK2 causes both a ciliogenesis defect in ciliated cells and a centrosomal cohesion deficit in dividing cells [36,41] (Figure 1). Centrosomal cohesion deficits can be detected in peripheral cells from LRRK2-PD patients as compared with healthy controls [42], and this may help to stratify sporadic PD patients with elevated LRRK2 kinase activity. This is in contrast with assays aimed at detecting differences in phospho-Rab10 levels from peripheral patient-derived material by Western blotting techniques, perhaps due to the biological variability of human samples combined with a modest increase in LRRK2-mediated Rab phosphorylation [42–45], and highlighting the need for methods characterized by higher sensitivity [11,33,46,47]. Importantly, and apart from the centrosomal cohesion deficits detected in peripheral cells from LRRK2-PD patients, ciliogenesis defects have been observed in striatal cholinergic interneurons and astrocytes in the intact brains of G2019S-LRRK2 and R1441C-LRRK2 knockin mice [38,48] as well as in certain brain areas from sporadic PD patients [49]. Further work is warranted to understand the cell type specificity and disease relevance of these findings.

Apart from RILPL1 and RILPL2, phospho-Rab8 and phospho-Rab10 also bind to JIP3 and JIP4, two proteins which serve as adaptors for both dynein and kinesin motors [50]. In cultured cells endogenously

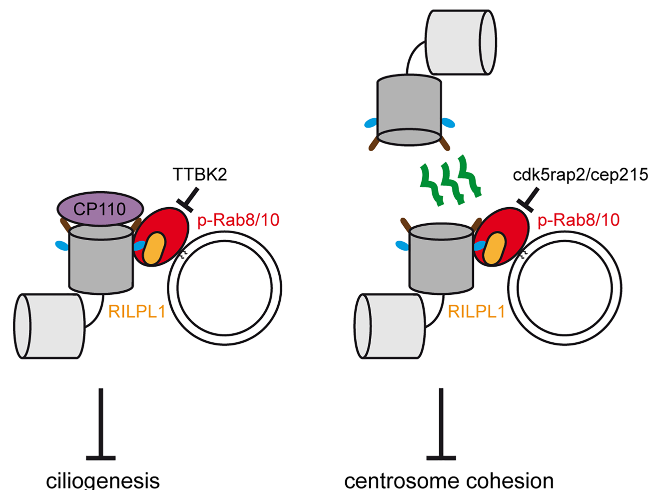

Figure 1. The phospho-Rab10/RILPL1 complex causes both ciliogenesis and centrosomal cohesion deficits.
Left: RILPL1 (orange) binds to unknown binding partner(s) at the subdistal appendage of the mother centriole (blue). Phosphorylated Rab8 and Rab10 (red) are localized on vesicles close to the centrosome (e.g. vesicles from the pericentriolar endocytic recycling compartment or perinuclear damaged lysosomes) which allows for their binding to RILPL1. The centriolar phospho-Rab/RILPL1 complex interferes with the appropriate recruitment of tau tubulin kinase 2 (TTBK2) such that CP110 cannot be displaced from the mother centriole for ciliogenesis to occur. Right: the same centriolar phospho-Rab/RILPL1 complex interferes with the centriolar localization of cdk5rap2/cep215. In the absence of appropriate cdk5rap2 localization, when centrosomes are duplicated during G2 of the cell cycle they cannot be held in close proximity to each other, resulting in a centrosomal cohesion deficit. Light gray, daughter centriole; dark gray, mother centriole; brown, distal appendage of mother centriole; blue, subdistal appendage of mother centriole; green, linker proteins critical for appropriate cohesion of duplicated centrosomes in G2 phase of the cell cycle.

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expressing pathogenic LRRK2, phospho-Rab10 has been detected on autophagosomes where it recruits JIP4 and the anterograde motor protein kinesin-1, causing defective retrograde axonal transport and maturation of autophagosomes [51]. In the cell body, lysosomal damage triggers LRRK2-mediated phospho-Rab10 accumulation at the lysosomal membrane, followed by recruitment of JIP4 and lysosomal tubule formation and vesiculation [52,53]. Finally, upon induction of lysosomal overload stress, phospho-Rab8 and phospho-Rab10 have also been described to accumulate on lysosomes to recruit the effector proteins EHBP1 and EHBP1L1 [54]. The precise consequences of these different phospho-Rab/effector protein complexes for lysosomal health remain to be determined. Similarly, it remains unclear whether the different phospho-Rab/effector protein complexes coexist in a given cell type under steady-state conditions or upon lysosomal stress, and how the effects on ciliogenesis, autophagosomal transport and lysosomal tubulation/vesiculation may be inter-related. Finally, whilst autophagic and lysosomal alterations have been reported in the brains of G2019S-LRRK2 knockin mice [55–57], it remains unknown whether these deficits are phospho-Rab-dependent and whether they involve the effector complexes and mechanisms as described *in vitro*.

LRRK2 localization and activation

Biochemical studies have shown that endogenous wildtype LRRK2 is mostly found in the cytosol where it exists as a relatively inactive monomer, whilst membrane association causes dimer/tetramer formation and increases the LRRK2 kinase activity [58,59]. However, the precise subcellular localization of endogenous wildtype or pathogenic mutant LRRK2 remains unknown. Upon transient overexpression, R1441C-LRRK2 and Y1699C-LRRK2 but not G2019S-LRRK2 associate with a type of microtubules [60,61] composed of non-conventional 11 or 12 protofilaments [62–64]. These protofilaments imply spiral trajectories for cargoes, which may pose challenges to directional transport, especially in dense cellular environments [65]. In addition, LRRK2 has been reported to interact with regulators of both the microtubule and actin cytoskeleton [66–69]. Therefore, it is possible that certain pathogenic LRRK2 mutants associate with non-conventional microtubules such as those proximal to the centrosome and a Rab10-positive membrane compartment to trigger Rab10 phosphorylation due to their spatial proximity to substrate, without an inherent increase in kinase activity *per se*.

Apart from structural insights into the LRRK2-microtubule interaction, recent full-length structures of monomeric or dimeric inactive LRRK2 and of a Rab29-induced tetrameric active LRRK2 complex highlight how membrane association mediated by Rab29 may cause LRRK2 activation [70–72]. Whilst overexpression of Rab29 can recruit and activate LRRK2 at membranes [23,73–76], endogenous Rab29 is not required for basal or stimulated LRRK2 kinase activity [15]. Therefore, Rab29-independent mechanisms must exist to activate endogenous LRRK2 at membranes. Interestingly, recent data suggest that the membrane recruitment of LRRK2 is facilitated by its own kinase activity in a feed-forward cooperative manner, whereby the phosphorylated Rab protein favors further LRRK2 recruitment and Rab phosphorylation [77]. In this context, LRRK2 activation is expected to preferentially occur at membranes where the endogenous Rab substrates reside.

Rab10 has been localized to distinct organelles including recycling endosomes, the trans-Golgi network or the endoplasmic reticulum, suggesting that its localization may be cell type-specific [78–80]. Importantly, and at least in some cell types, both Rab8 and Rab10 localize to a tubular perinuclear recycling compartment which is in direct contact with the centrosome [81–83]. Hence, the generation of phospho-Rab8/10 at such pericentriolar endocytic recycling compartment will allow for binding to centriolar RILPL1, followed by the centrosomal cohesion and ciliogenesis defects as described above. Similarly, and given the close apposition between the Golgi complex and the centrosome [84], the Rab29-mediated recruitment of LRRK2 to the Golgi complex may generate phospho-Rab8/10 proximal to centriolar RILPL1 which subsequently causes centrosomal defects via the phospho-Rab/RILPL1 nexus [74].

LRRK2 can also be recruited to distinct endomembranes classically devoid of endogenous Rab8/10 such as phagosomes, autophagosomes and damaged endolysosomes [51,52,54,85,86]. In those cases, the cooperative LRRK2 recruitment may be mediated by Rab35, another LRRK2 kinase substrate which is known to localize to at least some of these organelles [87–89]. Once activated at those membranes via a cooperative mechanism, LRRK2 may then cause accumulation of additional phospho-Rab substrates given their inability to be extracted from membranes by GDI, culminating in lysosomal tubulation/autophagosome trafficking defects via a phospho-Rab10/JIP4 effector complex. However, and at least in the case of lysosomes, LRRK2 recruitment does not cause an indiscriminate accumulation of all phosphorylated Rab substrates on the same organelles. Rather, phospho-Rab10 seems to accumulate only on perinuclear lysosomes, with phospho-Rab12 accumulating on perinuclear but also on peripheral lysosomes [90]. Thus, additional mechanisms related to Rab dephosphorylation

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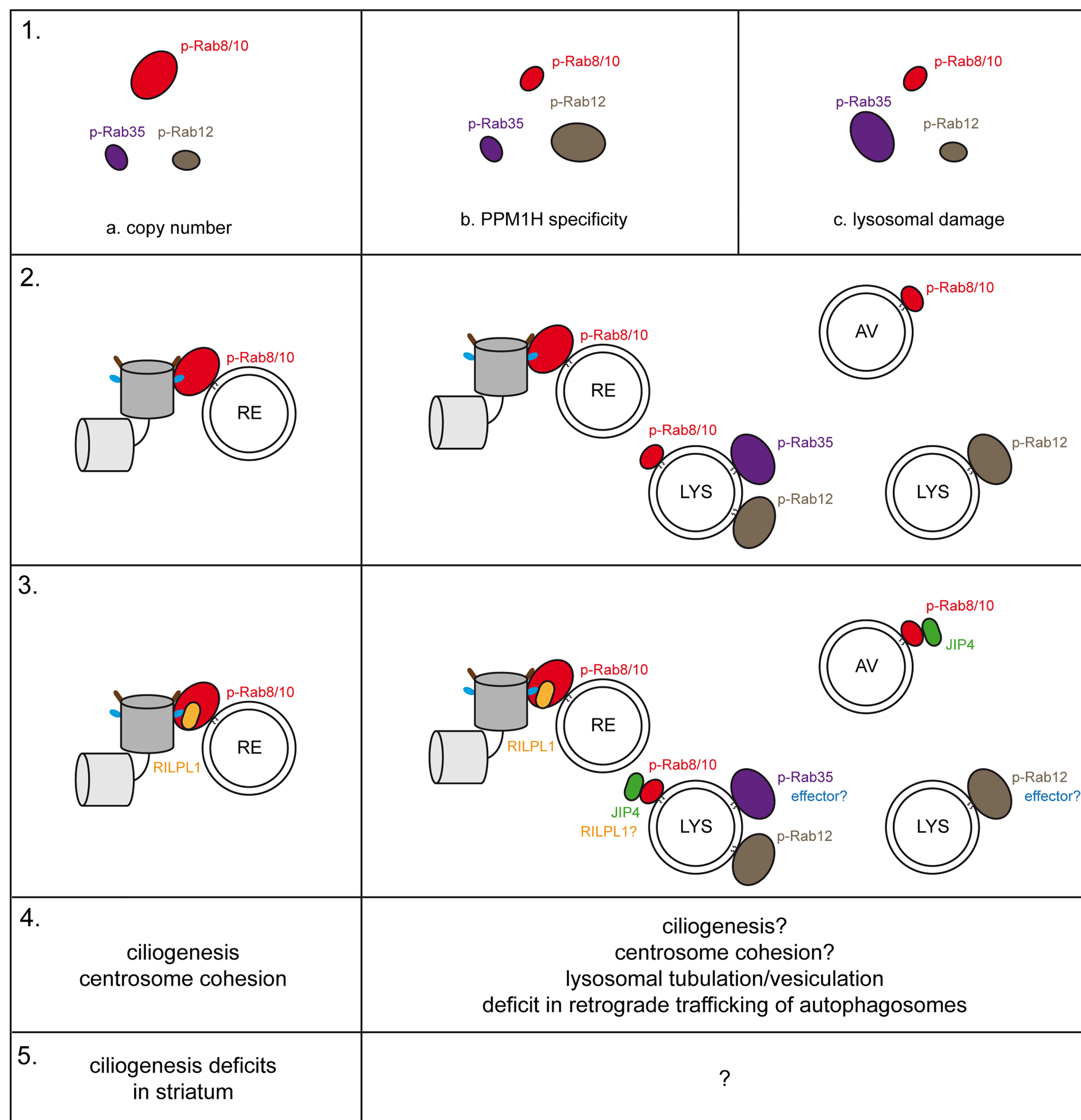

Figure 2. Major open questions related to cellular consequences of LRRK2-mediated Rab phosphorylation. Part 1 of 2
1. In a given cell type, the Rab substrate(s) most prominently phosphorylated may reflect their relative abundance (a. copy number), the presence of phosphatase(s) dephosphorylating only a subset of phospho-Rabs (b. PPM1H specificity), or the presence of certain triggers to favor phosphorylation of a subset of Rabs (c. lysosomal damage). **2.** In a given cell type, phospho-Rab8/10 localized to pericentrosomal vesicles from a tubular endocytic recycling compartment (RE) may prominently accumulate at the centrosome/ciliary base. In another cell type, phospho-Rab8/10 may accumulate at the centrosome/ciliary base, or phospho-Rab10 on autophagosomes (EV) in axons, or phospho-Rab10 and phospho-Rab35 on perinuclear lysosomes (LYS), or phospho-Rab12 on perinuclear and peripheral lysosomes. **3.** Dependent on phospho-Rab identity and subcellular localization in a given cell type, phospho-Rab8/10 on RE interacts with centriolar RILPL1. On perinuclear lysosomes and on autophagosomes, phospho-Rab10 interacts with JIP4. The effectors for phospho-Rab35 and phospho-Rab12 remain unknown. **4.** Dependent on cell type and under basal conditions, the phospho-Rab/RILPL1 complex causes deficits in ciliogenesis and centrosome cohesion. Upon lysosomal damage, a phospho-Rab10/JIP4 complex causes lysosomal tubulation and vesiculation in the cell body. A phospho-Rab10/JIP4 complex in the axon causes deficits in the retrograde trafficking of autophagosomes. How these different cellular outcomes may be inter-related remains unknown. **5.** In the intact mouse brain of mutant LRRK2-knockin mice, ciliogenesis deficits are observed in cholinergic interneurons and in astrocytes of the striatum. Whether the alterations in

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Figure 2. Major open questions related to cellular consequences of LRRK2-mediated Rab phosphorylation. Part 2 of 2
lysosomal functioning or autophagic transport are also reflected by cellular alterations in the intact mouse brain, and whether ciliogenesis and/or lysosomal dysfunction are present in other cell types and brain regions remains unknown.

and/or lysosomal positioning may contribute to the selective accumulation of only certain phospho-Rab proteins on distinct membranes. Finally, apart from either a Rab29-mediated or a cooperative phospho-Rab-mediated recruitment, other mechanisms related to phospholipid composition [91] and/or intraorganellar calcium [85] may contribute to the selective recruitment and activation of LRRK2 at distinct endolysosomal membranes. Since membrane recruitment results in LRRK2 activation and substrate phosphorylation, further work is warranted to understand the precise cellular triggers for LRRK2 activation at distinct intracellular membranes.

Conclusions

Recent biochemical, structural and cell biological work has nominated various mechanisms for pathogenic LRRK2 action *in vitro* and in the intact brain. Major unresolved questions include (Figure 2):

- What are the most prominent Rab substrates in a given cell type?
- Where do the distinct phosphorylated Rab proteins accumulate under basal conditions and upon induction of cellular stress in a cell type-specific manner?
- What are the main interaction partners of the phosphorylated Rab proteins at a specific subcellular site?
- What are the cellular consequences of these phospho-Rab/effector interactions in a given cell type, and do they coexist and/or influence each other?
- Which of the LRRK2-mediated alterations can be observed in the intact brain in a cell type-specific manner, and how do they contribute to disease pathogenesis?

Future work in this exciting research area hopefully will lead to a better understanding of how aberrant LRRK2 kinase activity causes PD.

Perspectives

- Point mutations in LRRK2 which increase its kinase activity cause PD, and LRRK2 phosphorylates a subset of Rab proteins.
- The phosphorylated Rab proteins accumulate in distinct subcellular membranes and interact with distinct effector proteins, suggesting multiple downstream cellular defects.
- One LRRK2-mediated phospho-Rab/effector complex seems to cause centrosome/cilia-related deficits *in vitro* and *in vivo*.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Author Contributions

S.H. and R.F. conceived and wrote the article, and Y.N. and B.B. provided intellectual input for the contents and edited the manuscript.

Abbreviations

COR, C-terminal of ROC; GDI, GDP dissociation inhibitor; GEF, GDP/GTP exchange factor; LRRK2, leucine-rich repeat kinase 2; PD, Parkinson's disease; ROC, Ras of complex.

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