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Review Article

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Rab GTPases as Physiological Substrates of LRRK2 Kinase

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LRRK2 (Leucine-Rich Repeat Kinase 2) is a gene whose specific mutations cause Parkinson's disease (PD), the most common neurodegenerative movement disorder. LRRK2 harbors GTPase and kinase activities, two enzyme activities that play critical roles in the regulation of cellular signal transduction. Among the several LRRK2 pathogenic mutations, the most prevalent G2019S mutation increases its kinase activity when compared with the wild-type (WT), suggesting that LRRK2 kinase substrates are potential culprits of PD pathogenesis. Although there were several studies to identify LRRK2 kinase substrates, most of them mainly employed in vitro kinase assays. Therefore, it remains uncertain whether the identified substrates were real physiological substrates. However, efforts to determine physiological LRRK2 kinase substrates have recently identified several members of the Rab GTPase family as physiological LRRK2 kinase substrates. A conserved threonine or serine in the switch II domain of certain Rab GTPase family members (Rab3A/B/C/D, Rab5A/B, Rab8A/B, Rab10, Rab12, Rab29, Rab35 and Rab43) has been pinpointed to be phosphorylated by LRRK2 in cells using sophisticated phosphoproteomics technology in combination with LRRK2-specific kinase inhibitors. The Rab GTPases regulate vesicle trafficking, suggesting that LRRK2 may be a regulator of such vesicle trafficking, confirming previously suggested LRRK2 functions. However, how the consequence of the LRRK2-mediated Rab phosphorylation is related to PD pathogenesis is not clear. This review briefly summarizes the recent results about LRRK2-mediated Rab phosphorylation studies.

Key words: LRRK2, Rab GTPase, Parkinson's disease, Kinase, Vesicle trafficking

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease, next to Alzheimer's disease and it affects 1%~2% of the population older than age 65 years [1]. The major symptoms of PD are related to movements such as resting tremor, rigidity, bradykinesia, postural instability and gait difficulty, although non-movement symptoms are also observed. Two main pathological hallmarks of PD are the degeneration of dopaminergic neurons in substantia nigra *pars compacta* and the formation of intraneuronal inclusions called Lewy Bodies (LB) [2]. The major risk factors of PD are oxidative stress and mitochondrial dysfunction which are often caused by exposure to certain environmental factors such as pesticides [3]. In addition, old age is considered as a risk factor for PD because aging gradually increases these risk factors [4]. Because of the rapid increase of the world's aging population, the number of PD patients and the social and economical burdens associated with PD are also rapidly increasing.

The incidence of PD is mostly sporadic, although in 5%~10% of cases, it is genetically inherited. More than 20 PARK loci have

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been mapped as loci corresponding to such inherited forms of PD (i.e., familial Parkinson's disease; FPD) [5, 6]. In the mid '90s, α-synuclein (SCNA) was reported as the first PD gene to cause PD upon its mutation to A53T or A30P [7, 8] and, subsequently, duplication and triplication of SCNA were also reported in some PD families [9-11], suggesting that the α-synuclein protein level is critical for PD pathogenesis. It is worthy to note that α-synuclein is mainly localized in the presynaptic terminals [12] and it is a major component of LB along ubiquitin [13]. Since the report of SNCA, several other genes have been reported as PD-causative genes with either an autosomal dominant or recessive mode of inheritance. A recent GWAS (genome-wide associated study) has identified 17 novel PARK loci in addition to the >24 PD risk loci already known [5]. In 2004, two groups reported LRRK2/dadarin (OMIM #607060), as an autosomal dominant PD gene corresponding to the PARK8 locus [14, 15] which was originally mapped on chromosome 12 through a study of a Japanese PD family [16].

LRRK2 as a PD causative gene

LRRK2 is a large protein of 2527 amino acids containing two functional enzymatic domains, the GTPase and the Ser/Thr kinase domains, and several protein-protein interaction domains such as the armadillo, ankyrin, leucine-rich repeat (LRR) and WD40 domains (Fig. 1) [17, 18]. LRRK2 is a member of the ROCO family that contains LRR, ROC (Ras of complex), COR (carboxyl terminal of ROC), and kinase domains [18, 19]. In humans, a homolog of LRRK2, LRRK1, is present as another member of the ROCO family, in addition to LRRK2 [20]. Although more than 30 DNA sequence variations of LRRK2 have been reported [21], only a few (N1437H, R1441H/C/G, Y1699C, G2019S, I2020T) was clearly identified as pathogenic mutations with two risk factors for sporadic PD (G2385R & R1628P) [6, 22-24]. Most of the pathogenic mutations are present in the functional domains, i.e., the ROC, COR, and Ser/Thr protein kinase (MAPKKK) domains, implying the crucial pathogenic functions of these domains for PD pathogenesis.

Among the several pathogenic LRRK2 mutations, the G2019S mutation is the most prevalent mutation and its identification [25-27] has been thought to be as important as the discovery of the SNCA pathogenic mutations because of the following reasons: (1) the G2019S mutation occurs in familial as well as sporadic PD patients. Especially in specific ethnic populations such as the Northern Arabs, up to 30% of sporadic cases have been reported to contain this mutation: (2) the symptoms of patients with the G2019S mutation are similar to those of idiopathic PD cases: (3) like sporadic PD, the G2019S mutation develops late-onset PD that PD occurrence increases with age. An estimated 28% of disease onset is at age 59, 51% at 69, and 74% at 79 years [28]: (4) Most importantly, the G2019S mutation clearly increases the kinase activity of LRRK2. These observations made a reasonable hypothesis that the increase of LRRK2 kinase activity is related to the mechanism of PD pathogenesis. Therefore, LRRK2 kinase activity could be a promising target for PD therapeutics development [29] and, so far, much effort to develop a LRRK2 kinase inhibitor as a drug to treat PD is going on in several global pharmaceutical companies [30, 31]. However, in the Asian population, the G2019S mutation was rarely observed. Instead, two risk factors, G2385R and R1628P, were observed with relatively higher frequencies [32-34]. It is also worth noting that the G2019S mutation exhibits incomplete

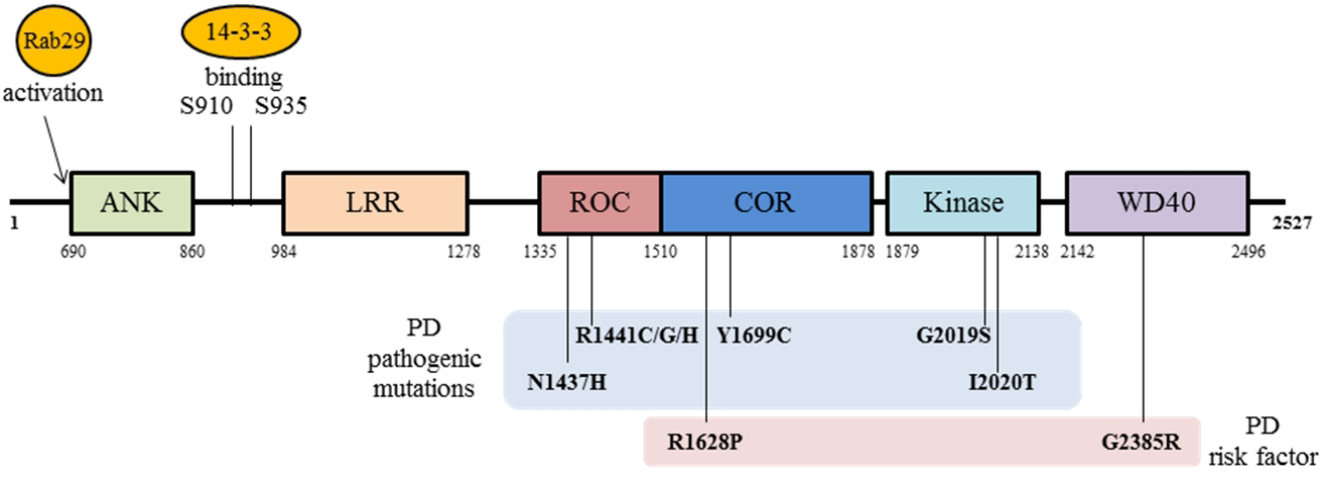

Fig. 1. A schematic view of LRRK2 with its pathogenic mutations and functional domains. ANK, ankyrin; LRR, Leucine-rich repeat; ROC, Ras of complex protein; COR, Carboxyl-terminal of ROC. Among numerous LRRK2-interacting proteins, two proteins are shown [86].

penetrance [28], implying that other factors such as aging and environmental elements are important in the pathogenesis of PD.

Another LRRK2 pathogenic mutation present in R1441 is the second most prevalent mutation in LRRK2 FPD cases [6, 14, 15]. Interestingly, the resulting amino acid from the R1441C mutation varies, and they include cysteine, glycine or histidine. The R1441C/G/H mutation is present in ROC, a GTPase domain, and, at least, the R1441C/G mutation has been reported to impair its GTPase activity along with another pathogenic mutation in the COR domain, the Y1699C mutation [35], again indicating the importance of LRRK2's enzymatic activities in PD pathogenicity.

More recent genetic information on LRRK2 mutations can be found in another excellent review by Monfrini et al. [6].

Because LRRK2 pathogenic mutations increase its kinase activity and cause PD, it is critical to know the *in vivo* phosphorylated protein targets of the LRRK2 kinase. Recently, several studies yielded promising results and this review aims to briefly summarize them. More detailed information about these studies can be found in other recent excellent reviews [23, 36-38].

Functions of LRRK2

LRRK2 is a big, multi-domain protein consisting of several protein-protein interaction and functional kinase and GTPase domains playing critical roles in the regulation of signal transduction. Therefore, it is of no surprise that LRRK2 plays regulatory roles in various cellular processes, such as autophagy, synaptic vesicle trafficking, protein synthesis, dynamics of microtubule and mitochondria, *etc.*, whose defects culminate to dopaminergic neuronal degeneration [17, 29, 39-41]. LRRK2 is ubiquitously expressed, mainly in the kidneys and lungs and it is relatively weakly expressed in the brain. LRRK2 localizes in the cytoplasm, often present in vesicles and cellular organelles [42].

Because PD is caused by defective mitochondria, an increase of oxidative stress, and impairment of protein quality control, the relationship of LRRK2 and autophagy is intensely being investigated. However, although it is obvious that LRRK2 regulates autophagy [43, 44], it remains unclear and controversial whether increased LRRK2 kinase activity positively or negatively regulates autophagy [41, 45]. Although recent *in vivo* studies using LRRK2 knock out or G2019S transgenic animals [46, 47] suggested that LRRK2 is a negative regulator of autophagy [48], further studies are needed for clear conclusions.

LRRK2 plays critical roles in synaptic vesicle trafficking. At first, LRRK2 was reported to interact with Rab5B to impair endocytosis of synaptic vesicles [49]. Subsequently, various studies suggested LRRK2's crucial functions in synaptic vesicle trafficking. For example, LRRK2 phosphorylates endophilinA at the S75 site to affect tubulation of synaptic vesicle membrane [50] as well as endocytosis of synaptic vesicles [51]. A further study showed that EndophilinA-induced macroautophagy is activated by LRRK2-mediated endophilinA phosphorylation [52]. Other studies suggested that the R1441C and the G2385R mutations differentially regulate phosphorylation of synaptic vesicle proteins and binding affinity to synaptic vesicle proteins, respectively [53-55]. In addition, LRRK2 silencing altered evoked postsynaptic currents and dynamics of synaptic vesicle recycling [56].

LRRK2's function in protein synthesis was also suggested by a study showing that the protein synthesis regulator eIF4E-BP is phosphorylated by LRRK2 and that this phosphorylation in a fly model increased protein synthesis, but also resulted in degeneration of dopaminergic neurons [57]. However, eIF4E-BP phosphorylation in the mammalian brain was not changed by LRRK2 expression [58]. Another study reported that LRRK2 pathogenic G2019S or I2020T mutation negatively controls microRNA-mediated translational repression and supported that LRRK2 mediates translation [59]. A more recent study showed regulation of protein synthesis by LRRK2-mediated phosphorylation of the ribosome protein S15 [60]. In this study, LRRK2-mediated S15 phosphorylation increased both cap-dependent and -independent protein translations [60]. However, our recent study suggested that the LRRK2 recombinant protein itself did not directly affect protein synthesis *in vitro* [61].

Defective mitophagy is another key mechanism in PD pathogenesis [62] and mutations in LRRK2 and other PD-causative genes such as Parkin and PINK1 resulted in mitochondrial impairment [63]. LRRK2 interacts with Dlp1/Drp1, a mitochondrial fission protein, and regulates mitochondrial dynamics, probably via LRRK2 kinase activity in neurons [64]. Recently, we have reported that LRRK2 kinase activity also facilitates mitochondria fragmentation in microglia [65]. Interestingly, one study has reported that mitochondrial DNA damage was also induced by LRRK2 kinase activity [66].

Another important function of LRRK2 is related to immunity. LRRK2 has been reported to be highly expressed in immune cells such as peripheral blood mononuclear cells [67, 68], suggesting its roles in immune function. LRRK2 has also been identified as a major susceptibility gene for inflammatory bowel disease (IBD [69, 70]). With respect to this function, lysozymes in Paneth cells of LRRK2 knockout mice were degraded in the lysosome, resulting in enteric infection [71]. Recent studies reported that LRRK2 kinase activity negatively regulates phagosome maturation [72] or facilitates phagocytic activity [73]. This discrepancy definitely requires a further study for LRRK2's roles in phagocytosis. Treatment of microglia with a TLR agonist such as LPS induced activa-

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tion of LRRK2 activity and co-treatment of LPS with a specific LRRK2 kinase inhibitor attenuated neuroinflammation response [74, 75], suggesting a role of LRRK2 in immune functions in the brain as well.

Interactions of LRRK2 with α-synuclein

α-Synuclein protein is the main component of LB and processing of α-synuclein monomers to aggregates via oligomers and fibrils is a main pathological mechanism of PD [76]. Along with LRRK2, SNCA is also an important autosomal dominant PD-causing gene. Accordingly, the pathogenetic relationship between LRRK2 and α-synuclein has been a topic of intense research. LRRK2 was reported to phosphorylate α-synuclein at S129 [77], but no other study confirmed this direct phosphorylation, although their co-localization in LB was reported [78]. Although results are still contradictory, the overexpression of G2019S in the brain of A53T transgenic mouse, an α-synuclein pathogenic mouse line, worsened several cellular processes related to PD, resulting in neurodegeneration [76, 79-80]. These results implied that the synergistic effect of LRRK2 and α-synuclein is cell type- or brain region-dependent because various studies reported that treatment with a LRRK2 kinase inhibitor decreases α-synucleinopathy [76]. At the same time, these results suggested that LRRK2 could regulate processing or cellular trafficking of α-synuclein. In fact, two recent reports showed that LRRK2 promotes exocytosis of lysosomal contents via phosphorylation of Rab proteins which may increase lysosomal secretion of toxic α-synuclein and α-synuclein propagation [81, 82].

LRRK2 kinase and its substrates

Earlier studies

Since after LRRK2's first two reports as a PD-causative gene [14, 15], identification of endogenous substrates of LRRK2 kinase has been intensively investigated [83, 84]. The first identified substrate was moesin, an ERM, actin binding cytoskeletal protein [85]. Subsequently, it was found that LRRK2 itself was auto-phosphorylated at S910 and S935 sites and these phosphorylation were essential for binding of the 14-3-3 proteins [86]. An early study reported that LRRK2 also interacts with and phosphorylated tubulin-associated Tau protein, whose aggregates are often identified in the brain of PD patients [87]. Another study reported that LRRK2 facilitates Tau phosphorylation by CDK5 [88]. These and other studies [89, 90] suggested that LRRK2 could modulate microtubule stability via regulation of Tau phosphorylation. In addition, other proteins such as eIF4E-BP, snapin, p53, akt1, endophilinA, ASK1, and p62 [50, 52, 57, 91-95] have been suggested as LRRK2 kinase substrates, although it remains unclear whether they are physiological substrates or not.

At first, to identify LRRK2 kinase substrates, LRRK2 interacting proteins were identified after co-immunoprecipitation assays or yeast two-hybrid screenings. Then, although mostly performed under non-physiological conditions, various cellular and biochemical assays were used to confirm whether the identified proteins were substrates of the LRRK2 kinase. However, after the development of specific LRRK2 kinase inhibitors and antibodies specific for phospho-substrates, it was possible to test LRRK2-mediated phosphorylation of endogenous proteins. Using this approach along with systemic proteomic analysis, several members of the Rab GTPase family were identified as endogenous substrates of the LRRK2 kinase [96, 97].

Rab Proteins as LRRK2 kinase substrates

Rab GTPases, a branch of the Ras superfamily, are critical regulators of intracellular vesicle trafficking [98]. It cycles an active GTP- and inactive GDP-bound forms and their membrane localization also affects its functional activity [99]. In addition, Rab GTPase activity was regulated by GEF, GAP, and GDI proteins [100]. Because cargo transport along a neuron's long axon is important for the neuron's viability, impairment of Rab proteins function at various intracellular membrane trafficking points is suggested to cause neurodegeneration [98]. The human genome encodes more than 60 Rab members, some of which, such as Rab5A, 5B and 5C, are close isoforms. Defective vesicle trafficking was suggested as a culprit of PD [101] and has also been reported in cells harboring PD-causative LRRK2 or SNCA mutations [56, 102, 103]. Among proteins functioning in vesicle trafficking, impairments of Rab proteins are suggested to be linked to PD [104, 105]. In addition, α-synuclein interacts with several members of Rab proteins and overexpression of these Rab proteins rescues defective vesicle trafficking caused by pathogenic α-synuclein [106, 107]. Moreover, Rab29 (Rab7L1) and Rab39B have been reported as putative PD-associated genes [108, 109] in addition to VPS35 [110], another vesicle trafficking regulator (Fig. 2).

Several elegant and systemic assays using phosphoproteomics and LRRK2 kinase inhibitors revealed that members of the Rab GTPase family are cellular physiological substrates of LRRK2 kinase [96, 97, 111]. Actually, the relationship of LRRK2 to members of the Rab proteins such as Rab7, Rab5B, and Rab29, suggests that LRRK2 pathogenic mutations dysregulate vesicle trafficking [49, 112, 113]. Mann and Alessi's groups [97] developed a stringent assay by combining G2019S MEF cells treated with or without specific LRRK2 kinase inhibitors and a phosphoproteomics approach to identify physiological LRRK2 kinase substrates. This

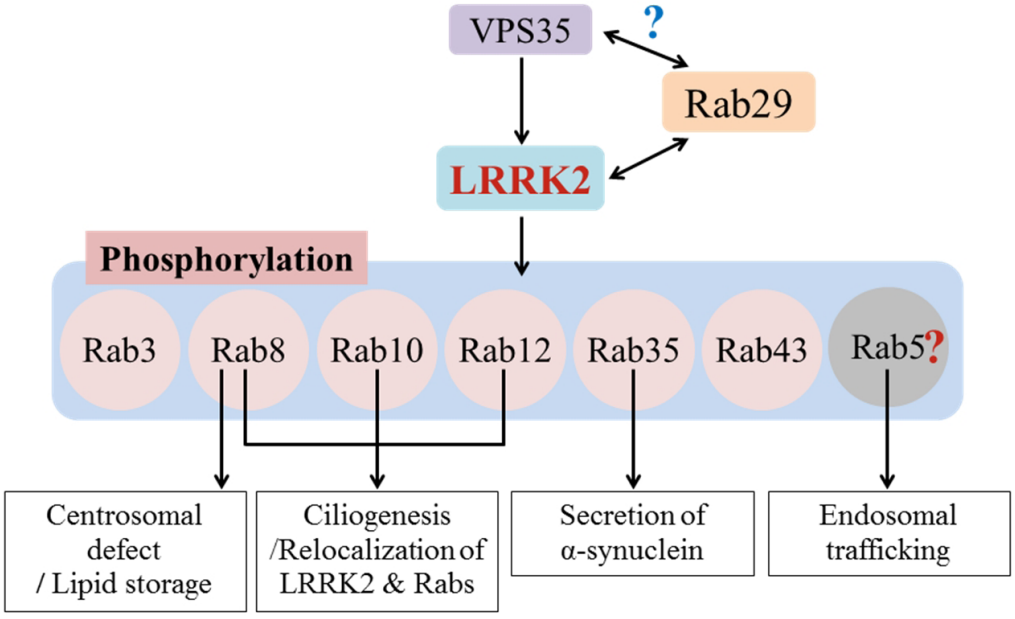

Fig. 2. A summary of consequences of LRRK2- mediated Rab phosphorylations. Two upstream regulators related to phosphorylation, VPS35 and Rab29 were shown [81, 117, 120]. Relationship between VPS35 and Rab29 is unknown yet. Among LRRK2 kinase substrates, Rab5 and Rab29 are putative substrates [96]. Activation of LRRK2 by Rab29 translocalizes LRRK2, Rab8, and Rab10 to lysosomal membranes, resulting in stabilization of Rabs on membranes after their phosphorylation [81].

elaborate study identified T73 of Rab10 and a known LRRK2 autophosphorylated site, S935, as LRRK2 kinase substrate sites. Because the T73 of Rab10 is present in the distinctive and highly conserved switch II domain of the Rab family members, they systemically tested all Rab GTPase protein members for their potential as LRRK2 kinase substrates and finally identified Rab3A/B/C/D, Rab8A/B, Rab10, Rab12, Rab35, and Rab43 as endogenous substrates and Rab5B/C and Rab29 as potential substrates [96]. The phosphorylated sites of these Rab proteins were Thr or Ser and these sites corresponded to the T73 site of Rab10 in the switch II domain [96]. They also reported that Rab interacting lysosomal protein like (RILP) 1/2 interacts with the phosphorylated forms of certain Rabs (Rab8, 10 or 12) and this interaction regulates ciliogenesis [96]. The phosphorylation of Rab35 by LRRK2 has also been confirmed [111]. Furthermore, a recent report suggested that LRRK2-mediated Rab35 phosphorylation positively regulates α-synuclein propagation, linking LRRK2 kinase activity to α-synuclein aggregate formation [82]. The most recent studies suggested lipid storage and centrosomal defect as functions changed after Rab8A phosphorylation by LRRK2 [114, 115]. Although various studies above have confirmed the LRRK2-meidated phosphorylation of Rab proteins, most of them were conducted in experimental settings. Therefore, whether this phosphorylation really occurs *in vivo* was an important question. A recent study has reported increased LRRK2 kinase activity and phosphorylated Rab10 level in dopaminergic neurons in the substantia nigra from brain tissues of patients with sporadic PD when compared with those of the control non-PD patients [116], suggesting that treatment with LRRK2 kinase inhibitor might be useful for not only PD patients carrying the LRRK2 mutations, but also PD patients without them.

Rab29 functions differently from other Rab proteins. Rather than just simple LRRK2 kinase substrate, Rab29 interacts with LRRK2 via the ankyrin (ANK) domain of LRRK2, localizes LRRK2 to the trans-Golgi network or the lysosome and activate LRRK2's kinase activity after its phosphorylation (Fig. 2) [81, 117-119]. Another vesicle trafficking regulator VPS35 has also been reported as a modulator of LRRK2 kinase activity. VPS35 D620N, a PD-associated pathogenic mutation, increases LRRK2-mediated phosphorylation of Rab proteins (Fig. 2) [120]. Therefore, these results have suggested that Rab29 and VPS35 function as upstream regulators of LRRK2 while Rab8/10/12/35 are LRRK2 downstream targets.

Moreover, a recent study showed that defective endolysosomal trafficking mediated by LRRK2 G2019S is partially caused by the impairment of Rab8A GTPase function [121]. As mentioned above, LRRK2 has also been reported to promote exocytosis of lysosomal contents via phosphorylation of Rab proteins which may increase lysosomal secretion of toxic α-synuclein and α-synuclein propagation [81, 82]. Altogether, these studies suggested that phosphorylation of Rab proteins to dysregulate vesicle trafficking is a major function of LRRK2, thus, obviously pointing out a strong functional relationship between LRRK2 and Rab GTPases.

However, there are still unanswered questions. For example, although ciliogenesis was decreased by pathogenic LRRK2 proteins via influencing of Shh signaling [96], defective ciliogenesis has not yet been observed as a major PD-associated symptom

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Table 1. A summary of Rab proteins phosphorylated by LRRK2

Rab proteins	Cellular phenotypes	Phenotypes of KO** or KD#
Rab3A/B/C/D	Exocytosis	QKO; die shortly after birth, respiratory failure
Rab5B/C*	Early endocytosis	KO: Loss of endosome, Failure of polarized cargo sorting
Rab8A/B	Endocytic recycling	SKO; Defect of microvillus and enlarged lysosomes in gut epithelial cells DKO; A ciliogenesis deficiency only under Rab10 KD
Rab10	Control of ER tubule fusion and extension, Endocytic recycling	KO: Embryonic lethal
Rab12	Endosomal lysosome sorting and degradation, Regulates autophagy	KD MEF†; Autophagy repression
Rab29 (Rab7L1)	Endosomal lysosome sorting and degradation	KO: A kidney lysosomal defect in an age-associated manner (mimic the LRRK2 KO)
Rab35	Recycling endosomal trafficking	KO: Preweaning lethality
Rab43	Phosphorylated by LRRK2	KO: Abnormal behavioral response to light

*RAb5B/C has been reported as putative kinase substrates. **KO, Knock-Out; SKO, Single Knock-Out; DKO, Double Knock-Out; QKO, Quadruple Knock-Out. #KD: Knock Down. †MEF: Mouse Embryonic Fibroblast.

and the spectra of patients with PD and those with ciliopathies are different [36], suggesting that functions of LRRK2-mediated phosphorylated Rab proteins other than ciliogenesis are related to PD. For example, does LRRK2-mediated phosphorylation of these Rab proteins affect their GTPase activities? Does phosphorylation change the functions or the binding affinities of Rabs to their various downstream effectors? It is highly possible that LRRK2-mediated phosphorylated Rab8/10/12/29/35 proteins alter their binding affinities to their various effector proteins in addition to RILP1/2 and EHBP1, thus altering the effect of functions regulated by these GTPases [81, 96, 118]. Although LRRK2-mediated Rab8 phosphorylation in SH-SY5Y cells was observed [115], most studies were performed in non-neuronal cells such as HEK 293 cells or MEF cells [96, 97]. Therefore, the most important question is whether this phosphorylation occurs in neurons and other brain cells such as microglia and astrocytes where LRRK2 expression is higher than that of neurons. The major functional outcomes by Rabs phosphorylated by LRRK2 were summarized in Fig. 2. The physiological functions of Rab proteins phosphorylated by LRRK2 kinase are briefly summarized in Table 1, and detailed information can be found in the excellent recent reviews [23, 36-38]. In addition to Rab proteins phosphorylated by LRRK2, other Rab proteins such as Rab1, Rab2, Rab7, Rab11A, Rab13, Rab32, Rab38 and Rab39B were also reported to be related to PD [98].

Phosphorylation of various Rab proteins by LRRK2 is now under intensive research to elucidate functional changes of phosphorylated Rabs related to PD pathogenesis. Further, such research may provide cues for PD therapeutic development.

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