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Invited Mini Review

Function and dysfunction of leucine-rich repeat kinase 2 (LRRK2): Parkinson's disease and beyond

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Mutations in leucine-rich repeat kinase 2 (LRRK2) are the most common cause of familial Parkinson's disease (PD). As such, functions and dysfunctions of LRRK2 in PD have been the subject of extensive investigation. In addition to PD, increasing evidence is suggesting that LRRK2 is associated with a wide range of diseases. Genome-wide association studies have implicated LRRK2 in Crohn's disease (CD) and leprosy, and the carriers with pathogenic mutations of LRRK2 show increased risk to develop particular types of cancer. LRRK2 mutations are rarely found in Alzheimer's disease (AD), but LRRK2 might play a part in tauopathies. The association of LRRK2 with the pathogenesis of apparently unrelated diseases remains enigmatic, but it might be related to the yet unknown diverse functions of LRRK2. Here, we reviewed current knowledge on the link between LRRK2 and several diseases, including PD, AD, CD, leprosy, and cancer, and discussed the possibility of targeting LRRK2 in such diseases. [BMB Reports 2015; 48(5): 243-248]

GENERAL BIOLOGY OF LRRK2

Implications from sequence analysis and homology modeling

In 2004, two independent research groups identified leucine-rich repeat kinase 2 (LRRK2) or dardarin as a causative gene for autosomal dominant familial Parkinson's disease (PD) in multiple ethic families (1, 2). LRRK2 gene encodes a large protein of 2,527 amino acids with multiple functional domains, including protein-protein binding domains such as ankyrin-like repeats, leucine-rich repeats, and WD40 domains, and enzymatic domains such as Ras of complex (ROC) GTPase domain, a carboxyl-terminal of Roc (COR) domain, and a kinase domain. To date, physiological and pathological functions of LRRK2 are mainly linked to its GTPase and kinase activities.

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On the basis of *in silico* sequence analysis and homology modeling, LRRK2 has been classified as a member of several protein subfamilies, such as ROC-COR (ROCO), mixed-lineage kinase (MLK), and receptor-interacting protein kinase (RIPK) families. On the basis of the well-defined cellular functions of such families, it is possible to predict plausible physiological and pathological functions of LRRK2. In mammals, the subfamily of ROCO, containing both ROC and COR domains, consists of four members, three of which are kinases, including LRRK2, its isoform LRRK1, and death-associated protein kinase (DAPK) (2). DAPK, a Ca^{2+}/calmodulin-regulated serine/threonine kinase, is implicated in the regulation of cell death, autophagy (3), cell adhesion and motility (4, 5), and inflammatory responses (6, 7). Loss of DAPK function was found in many primary cancer cells and cell lines, and the tumor progression and metastasis were inversely correlated with its expression (8). In addition to the homology of the ROC-COR domains in LRRK2 and DAPK, both kinases have been associated with the pathology of brain and neurodegenerative diseases. As mentioned above, *LRRK2* is a well-known PD gene, and genome-wide association studies showed that single-nucleotide polymorphisms in *DAPK1* are associated with late-onset Alzheimer's disease (AD).

LRRK2 encodes a kinase domain with high sequence homology to the MLK subfamily of mitogen-activated protein kinase (MAPK) kinase kinase (MAPKKK). MAPKKK activates extracellular signal-regulated kinase (ERK) 1/2, c-Jun N-terminal kinase (JNK), and p38 proteins (9); and MLK-mediated activation of JNK has been associated with PD pathology. In the postmortem brain of PD patients, phospho-JNK staining was detected in neurons adjacent to midbrain neurons with Lewy bodies (10). An inhibitor of MLK, CEP-1347 was under clinical trials for PD patients (11). CEP-1347 prevented JNK activation in neurons and showed neuroprotection in a variety of PD and neurodegenerative models, but the drug failed to show efficacy in clinical trials.

The kinase domain of LRRK2 is closely related to RIPKs, which have a role in the recognition of damage-, pathogen-, or stress-associated signaling. RIPK family consists of seven members, including LRRK1 and LRRK2 being designated as RIPK6 and RIPK7, respectively. RIPK1-5 proteins are related to immune signaling pathways (12, 13). Extracellular pathogens are

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recognized by leucine-rich repeat domains of nucleotide-binding oligomerization domain-containing proteins (NODs). NOD1 and NOD2 are components of the innate immune system and are involved in sensing the presence of pathogens. Upon pathogen recognition, NODs recruit RIPK, which triggers downstream signaling through the activation of NF-κB, resulting in the production of inflammatory cytokines. LRRK2 has also been implicated in inflammatory responses downstream of Toll-like receptor (TLR), which functions as an extracellular pathogen sensor, similar to NOD (14). Moreover, LRRK2 is known to regulate NF-κB activity and the production of cytokines and reactive oxygen species (ROS) in immune cells (15).

Implications from the expression and localization of LRRK2

LRRK2 is ubiquitously expressed in various tissues, and it is most abundant in the brain, the kidney, and the immune system. Expression of LRRK2 in various tissues implies that LRRK2 might have diverse roles. To understand physiological roles of LRRK2, several animal models have been developed. Studies from LRRK2 knock-out animals suggest that LRRK2 might play a part in synaptic transmission. In *Drosophila* models, LRRK2 mutants have impaired synaptic structures, such as synapse-overgrowth, expanded nerve terminal, and increased number of synaptic boutons (16). Such phenotypes are thought to result from dysfunction of protein synthesis, mitochondria transport, and microtubule polymerization. In LRRK2 knock-out mice, the number of mature spines is decreased and synaptic transmission is altered in striatal projected neurons (17).

In addition to brain dysfunction, abnormal phenotypes were found in the kidneys of LRRK2 knock-out mice (18-20). In the absence of LRRK2, aggregates of α-synuclein and ubiquitinated proteins were detected in the kidney; and autophagy-lysosomal pathway was also impaired, as indicated by the abnormal accumulation of lipofuscin granules and altered levels of LC3-II and p62, which are the markers for autophagy (18, 19). These studies suggest that LRRK2 might be involved in the regulation of protein homeostasis. It is unclear why the autophagic defect was found specifically in the kidney, but the higher expression level of LRRK2 in the kidney, possible compensation by LRRK1, the different rate of basal autophagy in distinct tissues, or a combination of such factors might provide an explanation.

LRRK2 is also highly expressed in immune cells, such as B-lymphocytes, monocytes, dendritic cells, and macrophages (14, 15, 21, 22). In the peripheral blood mononuclear cell population, LRRK2 is highly expressed in mature or activated monocytes, and the inhibition of LRRK2 has been shown to block monocyte maturation (21). Moreover, expression of LRRK2 could be upregulated in response to IFN-γ and LPS in monocytes and macrophages (14, 21, 22). These results suggest that LRRK2 might be involved in monocyte maturation and innate immune responses.

LRRK2 IN HUMAN DISEASES

Pathogenic mutations in *LRRK2* are the most prevalent genetic cause of PD, but growing evidence suggest that *LRRK2* is implicated in other seemingly unrelated human diseases, such as inflammatory diseases, leprosy, and several types of cancer. However, the pathological functions of LRRK2 in such diseases are unclear. The following sections describe current knowledge on the linkage between LRRK2 and multiple human diseases, based on possible cellular functions of LRRK2 including regulation of cytoskeletal reorganization, vesicle trafficking, protein synthesis, protein homeostasis, autophagy, and inflammation.

Parkinson's disease

PD is the most popular neurodegenerative movement disorder characterized by resting tremor, bradykinesia, posture instability, and rigidity. General pathological features of PD include progressive loss of dopaminergic neurons in the substantia nigra and the presence of Lewy Bodies (LBs), intraneuronal abnormal protein deposits. Although etiology of PD is not clearly understood, multiple genetic risk loci have been identified. Mutations in *LRRK2* are the most popular genetic cause of PD, accounting for 4% of familial PD and 1% of sporadic PD across all populations. Carriers with pathogenic mutations in *LRRK2* possess typical, idiopathic PD with few clinical differences from non-carrier patients, and they develop various neuropathological features ranging from pure nigral degeneration without LBs to nigral degeneration with LBs (in brain stem or widespread), ubiquitin-positive inclusions or neurofibrillary tau-positive tangles (2, 23). Mutations in a single gene can bring about multiple pathological consequences.

The pathological functions of LRRK2 have mainly been associated with aberrant kinase activity. In general, high kinase activity of LRRK2 pathogenic mutants have been linked to pathological features of PD, such as dopaminergic neuronal cell death, impaired dopamine neurotransmission and locomotive activity, defects in protein synthesis and degradation, inflammatory responses, and oxidative damage (24-27). Therefore, identifying physiological substrates of LRRK2 kinase has been the subject of extensive investigation to provide explanation for the disturbed cellular functions of LRRK2 as well as to develop possible therapeutic interventions for the disease.

Synaptic dysfunction and aberrant kinase activity of LRRK2 have been reported in several animal models of PD. Recently, a study has suggested a role for LRRK2 at the synapse and provided evidence that endothilin A (EndoA) is a direct target of LRRK2 kinase activity (28). EndoA is a protein harboring a Bin/Amphiphysin/Rvs (BAR) domain that interacts with membranes and induces membrane deformation. In a *Drosophila* model, LRRK2 has been shown to affect synaptic transmission by phosphorylating EndoA, and consequently, control membrane deformation and endocytosis of synaptic membrane at *Drosophila* neuromuscular junctions.

LRRK2 has also been shown to phosphorylate eukaryotic initiation factor 4E (eIF4E)-binding protein (4E-BP) and ribosomal protein S15 (RPS15). Evidence for LRRK2-mediated phosphorylation of 4E-BP and RPS15 raised the possibility that LRRK2 might play a part in the regulation of protein synthesis (24, 29). LRRK2-induced phosphorylation of 4E-BP dissociates 4E-BP from eIF4E, and thereby increases free eIF4E available for initiation of translation. It is plausible to suggest that increased and perhaps uncontrolled translation increases toxicity. Phosphorylation of RPS15 stimulates both cap-dependent and -independent mRNA translation, and thereby induces a bulk increase in protein synthesis, which again might induce neural toxicity.

In addition to protein synthesis, LRRK2 has also been implicated in the autophagy-lysosomal pathway. In animal and cell models of pathogenic LRRK2 mutants and in fibroblasts derived from PD patients with G2019S mutation, ubiquitinated proteins were aberrantly increased and enlarged aggregates of lysosomes were detected (30, 31). LRRK2 has also been shown to affect Rab7-dependent perinuclear lysosome clustering and lysosomal degradation (32). In addition, evidence for deregulation of autophagy has been provided by examining the brains of PD patients. Markers for autophagy were altered and autophagic vacuoles were accumulated in LRRK2 patient-derived cells (33). These lines of evidence suggest that impaired protein synthesis and degradation of the autophagy-lysosomal pathway might be responsible for LRRK2 pathology.

Alzheimer's disease

AD is the most common neurodegenerative disease showing progressive and irreversible loss of memory and cognitive functions, ultimately leading to dementia and death. General pathological features of AD include the presence of amyloid β plaques and intraneuronal tangles of hyperphosphorylated forms of microtubule-associated protein Tau. In general, clinical symptoms of PD and AD are quite distinct, but PD and AD share some common pathological features, such as abnormal protein deposits. More than 50 percent of AD patients have α-synuclein-deposited LBs and tau deposits as in PD patients (34). Especially, α-synuclein is involved in the pathogenesis of AD. The level of α-synuclein was increased in the brain of AD patients as compared with age-matched control brains (35). In the early stages of AD, α-synuclein is accumulated in presynaptic termini, implicating that aberrant deposits might be involved in the early events of AD pathogenesis (36). Furthermore, LBs and Lewy neurites are detected in the brains of AD patients (37). The expression analysis revealed that α-synuclein and LRRK2 mRNA levels were significantly increased in the temporal cortex of LBs variants of AD (LBV/AD) brains as compared with AD controls (38). Furthermore, α-synuclein aggregation was increased in aged, LRRK2-null mice as compared with age-matched control (18, 39); and α-synuclein-mediated cytotoxicity was exacerbated in α-synuclein A53T and LRRK2 G2019S double transgenic mice as compared to α-synuclein A53T mice (39). These results suggest that LRRK2 regulates α-synuclein-mediated Lewy pathology in AD. Previous studies suggest that LRRK2 might be involved in tauopathies, which include AD. Pathogenic mutants of LRRK2, G2019S, and I2020T have been shown to directly phosphorylate Tau at Thr181, depending on the association between LRRK2 and β-tubulin (40); and in LRRK2 R1441G transgenic mouse brains, Tau phosphorylation was elevated (41). Increased Tau phosphorylation has also been detected in postmortem brains of PD patients with LRRK2 mutation (2). Hyperphosphorylated Tau is a general pathological feature of AD patients. Phosphorylated forms of Tau dissociate from tubulin and preferentially self-aggregate to form intraneural tangle, which is associated with neuronal toxicity and AD pathology. Despite the molecular and cellular connections between proteins involved in AD pathology and LRRK2, LRRK2 mutations are not common among AD patients. To date, pathogenic mutations of LRRK2 found in PD have not been found in AD of various ethnic groups. A genome-wide association (GWA) study failed to identify common genetic risk factors for PD and AD (42). Thus, LRRK2 might not be a direct genetic risk factor for AD, but LRRK2 appears to be connected with several key proteins involved in AD pathology. LRRK2 might regulate protein homeostasis through regulation of lysosomal and autophagy pathways in neurodegenerative diseases, such as PD and AD.

Inflammatory bowel disease

GWA studies for Crohn's disease (CD) and leprosy suggest possible association between LRRK2 and inflammatory diseases (43, 44). (*Leprosy will be discussed in the following section.*) CD is a chronic inflammatory bowel disease caused by dysfunction of immune response to commensal intestinal microbiota (45). Several single nucleotide polymorphisms (SNPs) in LRRK2 loci were identified as risk factors for CD (43). Moreover, LRRK2 mRNA level was highly increased in the inflamed biopsy sample, as compared to non-inflamed control from the same patient with CD; and LRRK2 protein was expressed in lamina propria macrophages, dendritic cells, and B lymphocytes (15). In general, LRRK2 is highly expressed in B lymphocytes, monocytes, and dendritic cells. Especially, LRRK2 has been implicated in monocyte maturation and in the production of inflammatory cytokines during the course of innate immunity. A study analyzing the pattern of LRRK2 expression in monocyte subpopulations has shown that LRRK2 expression is higher in mature $CD14^+CD16^+$ cells than in $CD14^+CD16^-$ monocytes (21). In addition, monocyte-maturing stimuli, such as IFN-γ, serum free condition, and cold stress induced LRRK2 expression, and pharmacological inhibition of LRRK2, by treating with small chemical inhibitors, attenuated monocyte maturation induced by IFN-γ (21). Of note, IFN-γ is a key cytokine in immune response and its concentration in plasma and intestinal mucosal are increased in CD (46, 47).

A previous study using LRRK2-deficient mice has provided insights into the pathological mechanism of LRRK2 in in-

flammatory bowel disease (48). LRRK2 negatively regulates NFAT1 activity by modulating its nuclear translocation. NFAT family comprises transcription factors that regulate innate immune response in T lymphocytes, macrophages, dendritic cells, and neutrophils. With the accompanying defects in NFAT signaling, LRRK2 deficient mice show hyperactive immune responses and enhanced susceptibility to dextran sulfate sodium-induced inflammatory bowel disease. Notably, kinase activity of LRRK2 had no effect on NFAT1 activation. In particular, the inflammatory bowel disease risk allele M2397 affected the protein level of LRRK2, but had no effect on the kinase activity. Given that LRRK2 dysfunction in PD is mainly associated with the aberrant kinase activity, LRRK2 pathology in PD and inflammatory bowel disease might involve distinct molecular players and cellular pathways.

Leprosy

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* (*M.leprae*). Host immune responses and several genetic factors have been suggested to influence the clinical spectrum of and susceptibility to leprosy. Through GWA studies, significant associations between leprosy and SNPs in the genes encoding histocompatibility complex class II DR, RIPK2, tumor necrosis factor superfamily 15, C13orf31, and NOD2 have been found, and a trend toward an association with SNPs in LRRK2 has been reported (44). A previous study has provided evidence that NOD2-mediated innate immune signaling is associated with the pathology of leprosy. NOD2 functions as a pattern recognition receptor that senses bacterial-cell-wall peptidoglycan and muramyl dipeptide motif (49). Upon ligand binding, NOD2 receptor recruits RIPK2, a kinase which has high homology with LRRK2 in the kinase domain. RIPK2 recruitment initiates intracellular signaling pathways, leading to the activation of NF-κB signaling and induction of downstream target genes. Mice lacking NOD2 or RIPK2 are highly susceptible to bacterial infection, owing to defects in the production of inflammatory cytokines that activate T lymphocytes. Exactly how LRRK2 is linked to the pathology of leprosy remains unknown, but TLR signaling pathway is likely to be involved. Similar to NOD2 signaling pathways, TLR-mediated signaling is also linked to leprosy, and TLR1, 2, and 4 have genetic associations with leprosy. TLRs mediate pathogen sensing during innate immune responses and TLR1, 2, and 6 are involved in *M. Leprae* antigen recognition (50). Notably, TLR2, 4, 5, 6, 7, and 9 agonists, which signal via MYD88 pathway, enhance phosphorylation of LRRK2 at Ser910 and Ser935, which is thought to represent the activation status of LRRK2 kinase activity in macrophages. However, NOD1 and NOD2 agonists failed to induce the phosphorylation of LRRK2 (14). Therefore, it is possible that LRRK2 is involved in the pathology of leprosy through TLR-mediated inflammatory signaling pathways, but not through NOD signaling. Together, these results suggest that specific inflammatory stimuli and pathological conditions regulate LRRK2 activity and functions in multiple immune diseases.

Cancer

Debate about the association between PD and cancer has a long history. Epidemiological studies suggest that PD patients are less susceptible to develop most types of cancers, but with some exceptions. However, since genetic factors of PD have been identified, the premise of cancer susceptibility in PD patients is changing. PD genes, such as *α-synuclein*, *Parkin*, *PINK1*, *DJ-1*, and *LRRK2* have been associated with particular types of cancer (51). *Parkin* was the first to be identified as a tumor suppressor gene among PD risk genes, and loss-of-function mutations in *Parkin* were found in several types of cancers. *DJ-1* has been shown to down-regulate the expression of a tumor suppressor gene, *PTEN*, and a high level of *DJ-1* was detected in various types of cancer. In several epidemiological studies, the most prominent pathogenic mutant of LRRK2, G2019S carriers showed increased incidence in nonskin cancers, hormone-related cancers, and breast cancers (52-54). In papillary renal and thyroid carcinomas, chromosomal amplification of LRRK2 was detected, and LRRK2 expression and receptor tyrosine kinase MET activity were highly correlated (55). Furthermore, depletion of LRRK2 disrupted the activation of MET and prevented tumor cell proliferation (55). Precise role of LRRK2 in cancer progression is yet to be defined, but a possible link might be found in the regulation of protein translation. LRRK2 interacts with eIF4E and directly phosphorylates 4E-BP. This eIF4E-4E-BP mediated protein translation controls a subset of mRNAs, including transcription factors *E2F* and *DP*, and phospho-4E-BP enhances their translation (56, 57). In mitotic and post-mitotic cells, E2F and DP heterodimerize and control cell fate in a distinct fashion. In mitotic cells, up-regulation of E2F-DP contributes to cancer progression by promoting cell proliferation, whereas in post-mitotic neurons, E2F-DP induces death. Notably, LRRK2 has been shown to negatively regulate the translational repression of E2F and DP through antagonizing miRNAs, *let-7* and *miR-184*, respectively (56). Therefore, LRRK2 might have a role in cancer progression through the regulation of eIF4E-4E-BP axis and miRNA-mediated protein translation. In addition to protein translation, regulation of autophagy and cytoskeletal rearrangement could play a part in LRRK2-mediated pathology in cancer.

CONCLUSION

Currently, it remains unclear how LRRK2 regulates the pathology of multiple, seemingly unrelated human diseases. LRRK2 is genetically associated with several diseases, implying that different mutations are associated with distinct pathology. Mutations can alter enzymatic activities of LRRK2 or the ability of LRRK2 to associate with its upstream regulators or downstream effectors. Indeed, pathogenic mutations linked to PD and cancer alter the kinase or GTPase activity of LRRK2; and accumulating lines of evidence suggest that enzymatic activities are critical to disease progression. However, mutations associated with immune dysfunction have little effect on the kin-

ase activity of LRRK2, and the pathology is not linked to its kinase activity. Therefore, each disease associated with LRRK2 might involve distinct pathological mechanisms. To evaluate LRRK2 as a therapeutic target in multiple diseases, it will be of importance to understand the functions and signaling of LRRK2 in multiple diseases.

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