LRRK2 Signalling Pathways in Parkinson’s Disease

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Abstract

Parkinson’s disease (PD) is a common neurodegenerative disorder with the pathological hallmark of progressive loss of dopamine neurons in affected brains. There is no cure for PD and current therapy does not halt the underlying degenerative process. The pathogenesis of PD is not fully understood but is likely caused by a combination of genetic and environmental factors. Several genes are associated with the onset and progression of familial PD. Mutations in LRRK2 are the most frequent known cause of late-onset PD. Many studies have been conducted to elucidate the functions of LRRK2 and identify effective LRRK2 inhibitors for PD treatment. In this review, I discuss the role of LRRK2 in PD and recent progress in studying LRRK2 cellular functions and the use of LRRK2 inhibitors as therapeutic agents.

Introduction

Parkinson’s disease (PD) was first described by Dr. James Parkinson in 1817 as a “shaking palsy” [1] is the second most common neurodegenerative disorder after Alzheimer’s disease (AD). PD affected 6.2 million people and resulted in about 117,400 deaths globally in 2015 [3], typically occurs in people over the age of 60, of which about one percent are affected [3], with an incidence of 1.7% in individuals aged over 65 years [4]. PD is characterized by the selective loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc) of the midbrain in affected brains. There is no cure for PD and current therapy does not halt the underlying degenerative process, although several clinical approaches, including levodopa treatment and deep brain stimulation, are currently used to manage the symptoms of PD.

Therefore, it is vitally important to elucidate the mechanisms underlying PD pathogenesis, to predict disease onset and provide scientific guidance for targeted therapy. Recent genetic studies have revealed an underlying genetic cause in at least 10% of all PD cases [5] which provides new opportunities for discovery of molecularly targeted therapeutics that may ameliorate neurodegeneration. Among the genes associated with PD, leucine-rich repeat kinase 2 (LRRK2) has emerged as the most relevant one to PD pathogenesis, since its mutations were identified in PD patients in 2004 [6,7]. More than 40 mutations of LRRK2 have been found in both familial and sporadic forms of PD [8,9], among which, a missense mutation, G2019S, is frequently found in not only familial but also sporadic Parkinson’s disease cases [10].

The G2019S mutation enhances kinase activity, suggesting that small molecule LRRK2 kinase inhibitors may be able to block aberrant LRRK2-dependent signaling in Parkinson’s disease [11,12]. In this review, I discuss the role of LRRK2 in PD pathogenesis and recent progress in the development of LRRK2 inhibitors for PD treatment.

LRRK2 Biology

LRRK2 is a large gene whose transcript encodes a 2527 amino acid protein (286 kDa) that is comprised of 51 exons. Sequence analysis predicts that LRRK2 contains multiple domains, including an armadillo repeats (ARM), an ankyrin-like (ANK) domain, leucine-rich repeat (LRR) domain, a Roco family of G-proteins comprising a Ras-of-complex (Roc) domain followed by its associated C-terminal of Roc (COR) domain, a mitogen-activated protein kinase (MAPK) domain and a C-terminal WD40 domain (Figure 1). The presence of both protein interaction domains (ARM, ANK, LRR and WD40) and the enzymatic domains (ROC and MAPK) within LRRK2 suggests that this protein may serve as a scaffold for assembly of a multiprotein complex and act as a central integrator of multiple signaling pathways. The multiple allosteric and enzymatic functions within one protein make LRRK2 an excellent therapeutic target. Several proteins, including ezrin/
radixin/moesin[13], 4E-BP[14], MKks [15,16], β- tubulin [17], α-synuclein[18], peroxiredoxin 3[19], Akt1[20] and ArfGAP1 [21,22], have been reported to be phosphorylated by LRRK2, and validated as non-physiological substrates of LRRK2. Recently, progress in studying cellular functions of LRRK2 has been made, that Ser1292 autophosphorylation occurs in vivo and is enhanced by several LRRK2 mutations and could be inhibited brain-penetrating LRRK2 kinase inhibitor [23]. Further, the role of LRRK2 in vesicular membranes could be mediated by the ability of LRRK2 to phosphorylate a subgroup of Rab GTPases, including including RAB8A (Thr72) and RAB10 (Thr73), at highly conserved sites located in the center of the effector binding motif[24,25]. However, the exact interplay between LRRK2 and Rab GTPases remains unclear. More elegant studies on the functional substrates of the LRRK2 kinase domain and their downstream signalling pathways are needed to understand the function of LRRK2 and its role in PD (Figure 1).

Figure 1: Schematic diagram of the domain architecture of LRRK2.


**LRRK2 as a Therapeutic Target**

Protein kinases have become one of the most important classes of drug targets in medicine, particularly in the field of oncology [26]. In the past decade, more than 20 different drugs targeting kinases have been approved for clinical use in humans for the treatment of various types of cancer [27]. LRRK2 kinase activity is critically linked to clinical effects, and the most prevalent PD mutation, LRRK2 G2019S in the kinase domain, enhances kinase activity by 2-4 folds [28]. LRRK2 kinase inhibitors are therefore being actively pursued. Some non-selective inhibitors including staurosporin, K252A and Su-11248 (Sunitinib) were found to inhibit LRRK2 with their IC50 values in nanomolar range [29,30]. ROCK inhibitors such as isoquinolinesulfonamides hydroxy fasudil and H1152, and the structurally unrelated Y-27632, have also been found to inhibit LRRK2 with similar efficiencies (low micromolar range) [30]. Recently, first-generation ‘tool’ inhibitors that exhibit excellent kinase activity with p.R1441C/G/H, p.Y1699C, p.G2019S, and p.I2020T) annotated on these domains. The regions and associated functions of the LRRK2 gene are also indicated.

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**Conflict of Interest**

No conflict of Interest.

**References**


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