Crohn’s and Parkinson’s Disease-Associated LRRK2 Mutations Alter Type II Interferon Responses in Human CD14⁺ Blood Monocytes Ex Vivo

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Abstract
The Leucine Rich Repeat Kinase 2 (LRRK2) gene is one of causative genes of familial Parkinson’s disease (PD). The M2397T polymorphism in LRRK2 is genetically associated with sporadic Crohn’s disease (CD). LRRK2 is expressed in human CD14⁺ monocytes, induced by interferon-γ (IFN-γ) and suppresses inflammatory activation. We hypothesize that IFN-γ-induced LRRK2 and inflammatory gene expression is altered by LRRK2 genetic polymorphism found in CD and PD cases. A total of 46 CD and 51 control cases, and 16 PD cases and 16 PD-linked LRRK2 mutation cases were recruited. Live human CD14⁺ monocytes were isolated from donors for ex vivo IFN-γ stimulation and gene expression analysis. IFN-γ potently enhanced TNFA, IL12, HLADRA1 and LRRK2 expression, which was suppressed by FK506, a calcineurin-specific inhibitor, but further enhanced by LRRK2-specific kinase inhibitor (GSK2578215A). The 2397-M/M CD risk allele enhanced IFN-γ responses of CD14⁺ cells in CD but not in control group. CD14⁺ monocytes from G2019S and R1441C LRRK2 mutated PD cases and carriers show no changes in IFN-γ responses for TNFA or IL12, reduced response for HLADRA1, and enhanced responses for LRRK2 in FK506-sensitive manner. These data demonstrate that CD-associated LRRK2 mutations are significant modifiers of innate immune response in CD14⁺ monocytes, and PD-associated LRRK2 mutation may contribute to reduced antigen presentation response.

Keywords Crohn’s disease · LRRK2 · Monocytes · Parkinson’s disease · Single nucleotide polymorphism · Type II interferon

Introduction
The Leucine Rich Repeat Kinase 2 (LRRK2) gene is a causative gene of familial PD (Cookson 2010). It has a kinase domain, which shares homology with the RIP and MKKK family of kinases (Cookson 2010). LRRK2 has been identified as the gene mutated most frequently in autosomal dominant familial Parkinson’s disease (PD). PD patients with LRRK2 mutations

Highlights
• IFN-γ induced LRRK2 and cytokine gene expression in human CD14⁺ monocytes ex vivo.
• GSK2578215A enhances IFN-γ responses to LRRK2 and inflammatory molecule gene expression.
• LRRK2 2397-M/M allele enhances IFN-γ responses in Crohn’s disease cases.
• Parkinson’s disease (PD)-linked LRRK2 mutations enhance IFN-γ-induced LRRK2 level.

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show clinically typical parkinsonism with neuropathology such as substantia nigral degeneration and Lewy bodies (Zimprich et al. 2004). However, in situ hybridization and Northern blotting results revealed surprisingly low signals for LRRK2 mRNA in brain, especially very low levels in critical PD sites including the SN (Zimprich et al. 2004; Galter et al. 2006).

LRRK2 is highly expressed in human peripheral blood mononuclear cells (PBMCs), especially in CD14+ monocytes (Hakimi et al. 2011). Multiple single-nucleotide polymorphisms (SNPs) in the LRRK2 locus also have been reported to be associated with inflammatory diseases including Crohn’s disease (CD) (Van Limbergen et al. 2009). LRRK2 is potently induced by type II interferon (IFN-γ) in human immune cells (Gardet et al. 2010; Thevenet et al. 2011) and suppress the activity of the transcription factor Nuclear Factor of Activated T cells (NFAT), which transcriptionally activates the expression of inflammatory genes (Liu et al. 2011; Vora and McGovern 2012). This suggests that LRRK2 provides negative feedback to inflammatory activation upon type II interferon–mediated inflammatory response through degradation of NFAT. IFN-γ is highly upregulated in CD patients, and is involved in the T-helper 1 immune response by CD4+ T cells (Fuss et al. 1996; Rafa et al. 2010). Mice lacking LRRK2 exhibit increased sensitivity to the zymozan-induced inflammatory response and experimentally induced inflammatory bowel disease (Liu et al. 2011). Finally, the 2397-M allele of M2397T polymorphism in LRRK2, which is linked to sporadic CD cases by GWAS, results in reduced LRRK2 protein expression. All these observation suggested that attenuation of negative feedback system to type II interferon–mediated inflammatory response is potentially involved in the pathogenesis of CD (Liu et al. 2011). The putative role of LRRK2 in immune function raises the possibility that LRRK2 contributes to PD by altering innate immune response to brain pathology. Transcriptional profiles of PBMCs from PD patients carrying the G2019S LRRK2 mutation show dysregulation in monocytic immune response pathway (Mutez et al. 2011).

In this study, we characterized how LRRK2 M2397T polymorphism affects CD14+ mononuclear cell activity in CD. We also demonstrated how LRRK2 kinase activity is responsible for the LRRK2-mediated inflammatory response in CD and PD with LRRK2 mutations. Our study shows the possibility that LRRK2 modify the disease progression through innate immune response.

Materials and Methods

Patient Recruitment and Ethics

After informed consent, 46 Crohn’s disease patients in remission state and 51 non-CD control patients without inflammatory conditions (Boston Medical center) and 16 LRRK2 PD mutant carriers and 16 non-carriers (Mayo Clinic, Florida) were recruited based on the clinical inclusion and exclusion criteria (Tables 1 and 2). During the sample preparation process, 6 cases were excluded due to low blood volume (n = 3) and low cell viability (n = 3) (Fig. 1A). The study was approved by the Mayo Clinic and BU Institutional Research Board.

Human Blood Collection and Isolation of CD14+ Mononuclear Cells

Human specimens were handled according to IRB approved institutional guidelines from Boston University School of Medicine and Mayo Clinic Florida. Fresh venous blood (30 mL) were collected using EDTA as an anticoagulant (BD Vacutainer, Franklin Lakes, NJ). The Mayo samples were delivered to the Boston University School of Medicine within 24 h of collection. PBMCs were isolated from the EDTA-treated whole blood by density gradient centrifugation using Ficoll-Paque and Leucosep tubes according to the manufacturer’s instructions (Miltenyi Biotech Inc., Auburn, CA). CD14+ mononuclear cells were affinity purified by microbeads by affinity purification by human CD14 microbeads (MACs system, Miltenyi Biotec, Fig. 2A-B).

Ex Vivo Stimulation

Isolated CD14+ mononuclear cells from whole blood samples obtained from Crohn’s and control patients (2.2 × 10^6 cells/sample) were stimulated by 100 IU/mL IFN-γ (R&D systems) ± 10 ng/mL NFAT inhibitor (FK506, Sigma-Aldrich) or LRRK2 inhibitors (1 μM GSK2578215A, GlaxoSmithKline Pharmaceuticals R&D). The reaction was stopped by addition

| Table 1 | Clinical inclusion/exclusion criteria for Crohn’s disease |
|---|---|
| Inclusion criteria | 1. Patients with 5-ASA, corticosteroid, AZA or 6-MP monotherapy  
2. Patients with 5-ASA + corticosteroid, AZA + corticosteroid dual therapy  
3. Age 18–75 |
| Exclusion criteria | 1. Patients with surgery within the past year  
2. Patients with fissure, ileus or intravenous hyperalimentation treatment  
3. Patients having more than three combinations of drug treatment simultaneously  
4. Patients on anti-TNF-α or MTX treatment  
5. Patients with active inflammation with serum CRP level of higher than 2  
5-ASA: 5-aminosalicylic acid; AZA: azathioprine; 6-MP: 6-mercaptopurine;  
TNF-α: tumor necrosis factor-α, MTX: methotrexate |
of Qiazol (Qiagen) at a 1:1 vol ratio and vortexing for 10 s to
denature RNase and protect total RNA from degradation,
followed by total RNA isolation (Qiagen). Flowchart of
CD14+ monocyte isolation, stimulation and RNA isolation.

Quantitative Real-Time Reverse Transcription PCR

Gene expression levels were quantified by real-time reverse
transcription PCR (RT-PCR, Mastercycler ep realplex 4s,
Eppendorf) using following primers. **TNFA**

F: 5'CCTCAAGGGACCTCTCTCTAAATC-3',
R: 5'ATGGGCTACTCAGGCTTGTCACT-3' (Stordeur et al. 2002),

**IL12** (p35)

F: 5'-CCTCAGTTTGGCCAGAAACC-3', 5'-GGTCTTTGC

TGAGGCCAGGC-3' (Riganò et al. 1999),

**HLADRA1**

F: 5'-GGACAAAGCCAACCTGGAAA-3', R: 5'-AGGACGTTGGGC

TCTCTTATTCC-3', 5'-CCTGAGGCTGTTCCTTCTTCC-3' (Corso et al. 2011),

**LRRK2**:

5'-CTTGGCTTGGTCCTTTATTTCC-3', 5'-CCTGAGGCTGTTCCTTCTTCC-3' (Milosevic et al. 2009),

**GAPDH**

5'-TCATCTCTGCCCCCTCTGCT-3', 5'-CGACGCCTGCTC

ACCACCCT-3' (Gardet et al. 2010).

**LRRK2 Genotyping**

A fraction of CD14 negative PBMCs were subjected to isola-
tion of genomic DNA and PCR direct sequencing of M2397T

allele. This is located in exon 9 (rs37618963) and corresponds
to a point mutation of coding sequence 7190 T > C (Fig. 2C).
PCR primers (PARK8_49F: 5'-CATAATGGTGGTGGTG

TGTCATG-3',

PARK8_49R: 5'-CTGTGACCCTCAGCAAGCC-3') produced a 451 bp ampiclon for the DNA sequencing of the target site (21).

Results

Enhanced IFN-γ Response in CD Group

Since LRRK2 is highly expressed in myeloid cells, we used
CD14+ monocytes isolated from PBMC using magnetic
bead cell isolation. The yield was approximately 2 × 106
CD14+ cells from 2.7 × 107 PBMC in 30-mL fresh whole
blood with more than 98% purity (Fig. 1B-C). Ex vivo stim-
ulation of CD14+ monocytes with IFN-γ induced gene ex-
pression of inflammatory cytokines (**TNFA** and **IL12**), major
histocompatibility complex molecules (**HLADRA1**), and
**LRRK2**, which was significantly suppressed by FK506
(Fig. 2), a specific inhibitor of calcineurin and known inhib-
itor of NFAT pathway via enhancing its phosphorylation-
dependent degradation (Liu et al. 2011). We also observed
enhanced induction of the tested inflammatory genes and
**LRRK2** itself by a potent LRRK2 specific kinase inhibitor
(GSK2578215A, Fig. 2) (Reith et al. 2012). Since LRRK2
is known to suppress NFAT signaling via its phosphoryla-
tion and proteasomal degradation, inhibition of LRRK2 ki-
nase activity may enhance NFAT-induced gene expression,
including LRRK2 itself. This finding also suggests that IFN-γ induction of LRRK2 is a negative-feedback system to control inflammatory signaling.

**LRRK2 M2397 Allele Enhances IFN-γ Response in CD Group**

We have genotyped CD risk SNP (rs37618963) on LRRK2 in CD and control cases (Table 3). As expected, LRRK2 2397-M allele is more prevalent than 2397-T allele in CD cases as compared to control cases, with odds ratio of 1.44. We compared the IFN-γ-induced gene expression of inflammatory molecules based on the LRRK2 locus rs37618963 polymorphism. There was no difference in IFN-γ response in control groups among rs37618963 alleles (closed columns, Fig. 3). Strikingly, 2397-T/M and 2397-M/M allele cases show enhanced IFN-γ-induced expression of TNFA, IL12 and HLA-DRA1 as compared to 2397-T/T allele in CD cases (open columns) but not in control cases (closed columns, Fig. 3), although LRRK2 expression was unaltered. GSK2578215A treatment enhanced gene expression of IL12, HLA-DRA1 and HLA-DRA1 as compared to 2397-T/T allele in CD cases (open columns) but not in control cases (closed columns, Fig. 3), although LRRK2 expression was unaltered. GSK2578215A treatment enhanced gene expression of IL12, HLA-DRA1 and

**Fig. 2** Gene expression analyses of IFN-γ stimulated CD14+ monocytes in CD cases. CD14+ monocytes from healthy control (Control, n = 51) and CD cases (n = 46) are subjected to ex vivo stimulation with 100 IU/mL IFN-γ in the presence or absence of FK506 and GSK2578215A (LRRK2-specific kinase inhibitor) for 4 h. The gene expression of TNFA, IL12, HLA-DRA1 and LRRK2 are examined. * or ** denotes p < 0.05 and 0.01 vs. controls with the same ex vivo treatment. †, ‡ or §§ denotes p < 0.05, 0.01 or 0.001 vs. unstimulated group of the same subjects. * or ** denotes p < 0.05 or 0.01 vs. IFN-γ-stimulated group of the same subjects as determined by one-way ANOVA with Tukey post hoc.

**Table 3** Demographics of CD and control cases

|                      | Crohn’s (n = 46)       | Control (n = 51)  |
|----------------------|------------------------|-------------------|
| Age                  | 47.26 ± 15.24          | 42.30 ± 15.20     |
| Gender (M/F)         | 28/21                  | 30/20             |
| LRRK2 M2397T         |                        |                   |
| MM                   | 8                      | 4                 |
| MT                   | 21                     | 23                |
| TT                   | 17                     | 24                |
| %M allele            | 40.22*                 | 30.39             |

*Odds ratio 1.44
**LRRK2** as compared to IFN-γ alone in both control and CD groups. Although 2397-M allele is shown to reduce LRRK2 protein levels, enhancement of LRRK2 expression in 2397-T/M and 2397-M/M allele CD cases by GSK2578215A treatment compared to 2397-T/T allele in CD cases (open columns) suggests enhanced LRRK2 kinase activity in 2397-T/M and 2397-M/M allele CD cases, which may result in augmentation of LRRK2 expression upon its kinase inhibition. These data show that 2397-M allele, a risk allele of CD, is a loss-of-function mutation and enhances IFN-γ-induced inflammatory response in CD group, and GSK2578215A treatment further augment the IFN-γ response both in control and CD groups.

**IFN-γ Response in CD14+ Monocytes from Sporadic PD and PD-Linked LRRK2-Mutated Cases**

We next performed a similar study using CD14+ monocytes isolated from sporadic PD (sPD) and PD-linked LRRK2-mutated (G2019S and R1441C) cases (Zimprich et al. 2004; Nandhagopal et al. 2008). Patients characteristics including LRRK2 M2397T polymorphism were shown in Table 4. Due to the limited sample volume per donor, we focused on the IFN-γ response in the presence or absence of FK506 in this cohort. IFN-γ-induced expression of TNFA and IL12 expression was unchanged between sPD (red column) and LRRK2-mutated cases (blue column), although both show potent suppression by FK506 (Fig. 4). Surprisingly, IFN-γ-induced expression of HLADRA1 levels were lower in LRRK2-mutated cases as compared to sPD cases, and is insensitive to FK506 treatment. IFN-γ-induced expression of LRRK2 was significantly enhanced in LRRK2-mutated cases as compared to sPD cases and sensitive to FK506. In contrary to CD-associated LRRK2 mutations, PD-linked LRRK2 mutations show little effect to IFN-γ-induced gene expression. This was unexpected, since PD-linked

![Fig. 3 LRRK2 M2397T allele-specific analysis of IFN-γ stimulated CD14+ monocytes in CD cases. LRRK2 M2397T allele-specific analysis of CD14+ monocyte gene expression of TNFA, IL12, HLADRA1 and LRRK2. * or ** denotes p < 0.05 and 0.01 vs. healthy control subjects with the same LRRK2 2397 allele and ex vivo treatment and # or ## denotes p < 0.05 or 0.01 vs. unstimulated group of the same subjects as determined by one-way ANOVA with Tukey post hoc.](image)

| Demographics of sPD cases and LRRK2 mutant carriers |
|------------------------------------------------------|
| **sPD (n = 16)** | **LRRK2 mutant (n = 6)** | **Carrier (n = 10)** |
| Age | 67.06 ± 12.26 | 71.67 ± 9.95 | 50.50 ± 10.05*<sup>**</sup> |
| Gender (M/F) | 8/8 | 4/2 | 5/5 |
| Lrrk2 M2397T | | | |
| MM | 2 | 0 | 1 |
| MT | 7 | 3 | 6 |
| TT | 7 | 3 | 3 |
| %M allele | 34.37 | 25 | 40 |

*<sup>**</sup>p < 0.01 vs. LRRK2 mutant PD
G2019S LRRK2 mutation is known to enhance kinase activity (Kelly et al. 2018), which would suppress inflammatory response and LRRK2 expression. The data suggests development of compensatory mechanism for IFN-γ-induced gene expression in PD-linked LRRK2 mutated cases.

**Discussion**

In this study, we have tested the effect of the LRRK2 mutations associated with CD and PD using freshly isolated human CD14+ blood monocytes for ex vivo stimulation with IFN-γ under the influence of NFAT-specific inhibitor (FK506) or LRRK2-specific kinase inhibitor (GSK2578215A).

In the CD Study, our findings are 1) IFN-γ response induces gene expression of TNFα, IL12, HLA DR1 and LRRK2 in CD14+ monocytes, 2) GSK2578215A enhances IFN-γ responses, while NFAT suppresses, 3) LRRK2 2397-M group show enhanced IFN-γ responses in CD group but not in the control groups, and 4) GSK2578215A further enhances IFN-γ responses regardless of M2397T allele. These data substantiate our hypothesis that LRRK2 is induced by IFN-γ and LRRK2 inhibition would enhance inflammatory gene expression. This function is impaired by CD-linked LRRK2 mutation in CD cases, presumably due to the nonsense RNA decay of LRRK2. Our recent study of the occurrence of CD with PD cohort identified only 2 cases of co-occurrence out 876 PD patients (0.2%), which is within the known prevalence of CD (26.0–198.5 cases per 100,000 persons) (Fujioka et al. 2017). A larger sample size is necessary to evaluate the effect of LRRK2 M2397M allele on the co-occurrence of CD and PD as a future study.

In the PD study, our findings are 1) IFN-γ-induced TNFα and IL12 expression was similar and sensitive to FK506 in sPD and LRRK2 mutated groups, 2) IFN-γ-induced HLA DR1 expression was reduced in LRRK2 mutated group and was insensitive to FK506, and 3) IFN-γ-induced LRRK2 expression was unexpectedly increased in LRRK2-mutated group and was sensitive to FK506. This suggests that PD-linked LRRK2 mutation may not have consistent effect for modulating IFN-γ-induced immune response as expected, but may affect antigen presentation in myeloid cells. Further study will be necessary to test the effect of ex vivo or systemic administration of LRRK2 inhibitors on enhancing HLA DR1 expression and antigen presentation machinery ex vivo or in vivo for evaluating its clinical application. For CD cases with 2397-M/M allele, specific LRRK2 activator may be beneficial for compensating the reduced activity of LRRK2 in myeloid cells in case chronic treatment with FK506 is inapplicable. In such a case, the drug would need a careful evaluation for the off-target effect of LRRK2 in other organs, such as kidney which have a high expression of LRRK2.

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**Compliance with Ethical Standards**

**Competing Interests** We declare no conflict of interest in this manuscript.

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**Fig. 4** Gene expression analyses of CD14+ monocytes in PD cases. CD14+ monocytes isolated from sporadic PD (sPD, n = 16) and PD-linked LRRK2 mutated cases (n = 16) were analyzed for gene expression of TNFα, IL12, HLA DR1 and LRRK2. * denotes p < 0.05 vs. sPD with the same ex vivo treatment and **#, ### or #### denotes p < 0.05, 0.01 or 0.001 vs. unstimulated group of the same subjects as determined by one-way ANOVA with Tukey post hoc.
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